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=> d his

     (FILE 'HOME' ENTERED AT 14:10:45 ON 16 JUL 2009)

     FILE 'CAPLUS' ENTERED AT 14:11:23 ON 16 JUL 2009
L1             1 S US 20070191339/PN
                 SELECT RN L1 1-

     FILE 'REGISTRY' ENTERED AT 14:11:47 ON 16 JUL 2009
L2             1 S E1

     FILE 'CAPLUS' ENTERED AT 14:12:03 ON 16 JUL 2009
L3            87 S L2
L4            74 S L3 NOT (2008/SO OR 2007/SO OR 2006/SO)

=> d l2
YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y)/N:y
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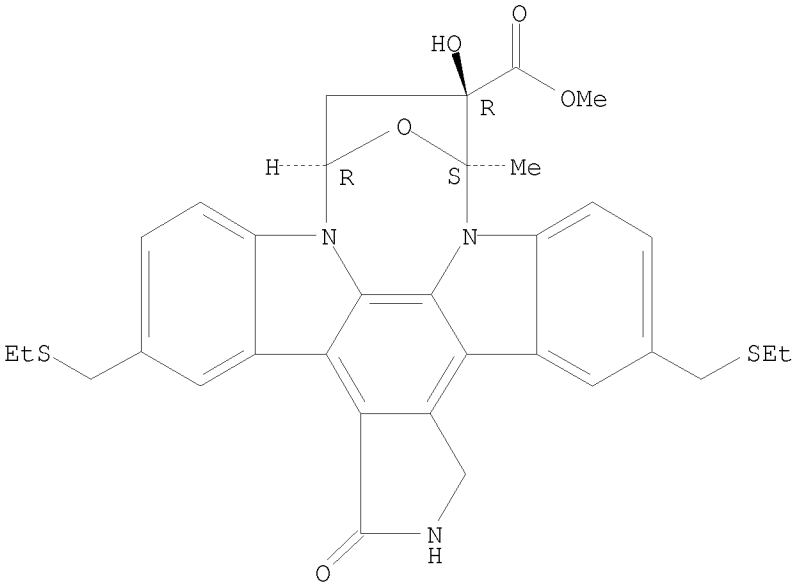
L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2009 ACS on STN
RN 156177-65-0 REGISTRY
ED Entered STN: 07 Jul 1994
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, [9S-(9α,10β,12α)]-
OTHER NAMES:
CN CEP 1347
CN KT 7515
FS STEREOSEARCH
DR 170587-65-2
MF C33 H33 N3 O5 S2
SR CA
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CIN, EMBASE, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, PHAR, PROMT, PROUSDDR, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

87 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
87 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L4 ANSWER 1 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2009:4555 CAPLUS
DOCUMENT NUMBER: 150:90475
TITLE: siRNA host cell kinase modulators as antivirals
INVENTOR(S): Mercer, Jason; Greber, Urs; Moese, Stefan; Helenius, Ari; Pelkmans, Lucas
PATENT ASSIGNEE(S): Eth Zurich, Switz.
SOURCE: PCT Int. Appl., 57pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009001224	A2	20081231	WO 2008-IB2644	20080620
WO 2009001224	A3	20090702		

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

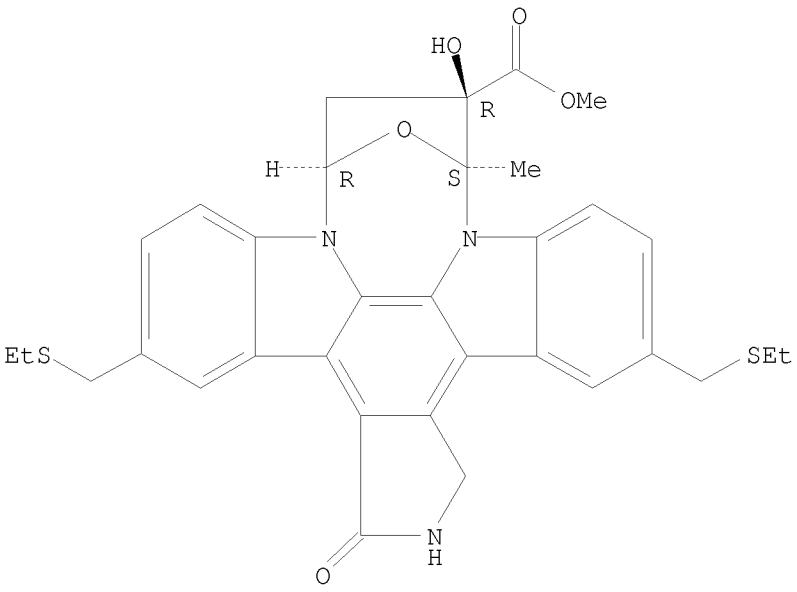
PRIORITY APPLN. INFO.: US 2007-945740P P 20070622

AB This invention provides methods for inhibiting or treating infection by viruses, in particular pox viruses by modulating a kinase, in particular by inhibiting a host cell kinase, involved in mediating viral infection. Methods to identify, validate, and classify the cellular proteins required by viruses during infection of host cells in order to select agents which can inhibit viral infection are described herein. Using a systems biol. approach the virus/host cell interaction is studied from initial attachment of the incoming virus to the cell surface, to entry, transcription, replication, biosynthesis, and assembly of progeny particles. The method employs a siRNA screening platform and uses gene silencing to map the 'viral infectome' - a compilation of cellular proteins that the virus needs to establish infection and drive the infectious cycle. Charting the infectome provides information on the viral biol. by the identification of host cell proteins involved in viral infection and allows the development of novel anti-viral drugs that prevent the viruses from establishing productive infection in cells.

IT 156177-65-0, CEP-1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(siRNA host cell kinase modulators as antivirals)

RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 2 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:1480570 CAPLUS
DOCUMENT NUMBER: 150:28974
TITLE: Mixed lineage kinases as drug targets in the treatment of stress-induced metabolic disorders
INVENTOR(S): Davis, Roger J.; Jaeschke, Anja
PATENT ASSIGNEE(S): University of Massachusetts, USA
SOURCE: PCT Int. Appl., 71pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008151323	A1	20081211	WO 2008-US66350	20080609

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

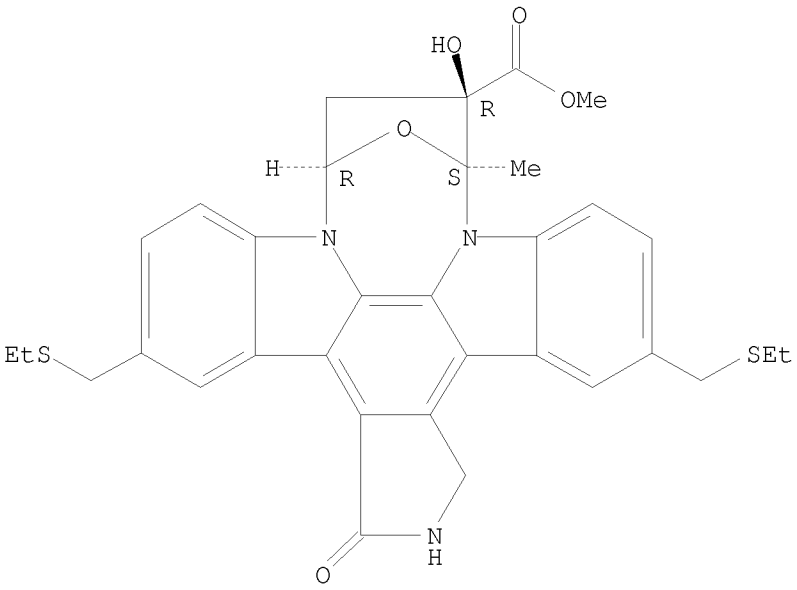
PRIORITY APPLN. INFO.: US 2007-933799P P 20070608

AB Methods of treating metabolic stress disorders by inhibition of mixed-lineage kinases are described. Mixed-lineage kinases are found to mediate the free fatty stimulation of JNK kinase. Insulin receptor substrate 1 is also shown to be a substrate for mixed lineage kinase 3. This enzyme is in turn activated by free fatty acid-activated protein kinase C isoenzymes. Methods of screening for inhibitors of the enzyme for therapeutic use and assays for the enzyme for diagnosis of metabolic disorders are described.

IT 156177-65-0
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as inhibitor of mixed-lineage kinases; mixed lineage kinases as drug targets in treatment of stress-induced metabolic disorders)

RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



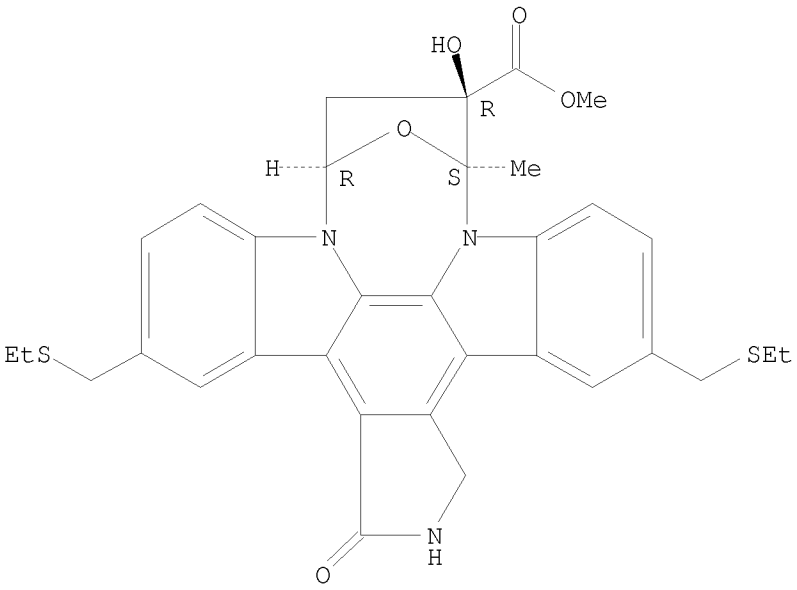
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:1211287 CAPLUS
DOCUMENT NUMBER: 149:440403
TITLE: Modulators for regulating autophagy, and therapeutic uses and combinations
INVENTOR(S): Bradner, James Elliot; Shen, John Paul; Perlstein, Ethan Oren; Rubinsztein, David; Sarkar, Sovan; Schreiber, Stuart L.
PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA; Dana Farber Cancer Institute; Cambridge Enterprise Ltd.
SOURCE: PCT Int. Appl., 159pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008122038	A1	20081009	WO 2008-US59129	20080402
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

PRIORITY APPLN. INFO.: US 2007-909640P P 20070402
OTHER SOURCE(S): MARPAT 149:440403
AB Autophagy is a cellular process by which cells canabalize non-essential cellular elements such as organelles to generate metabolites, or in some cases, to cause cell death. The invention provides modulators of autophagy, which have been identified using a high-throughput phenotypic screen of over 3500 compds. These modulators are useful in treating diseases ranging from proliferative diseases to neurodegenerative diseases to infectious diseases to protein misfolding states. Furthermore, the invention provides the treatment of proliferative disease such as cancer with a combination of autophagy inhibitors and protein kinase inhibitors.
IT 156177-65-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modulators for regulating autophagy, and therapeutic uses and combinations)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:737921 CAPLUS
DOCUMENT NUMBER: 149:76598
TITLE: Methods of diagnosis and treatment for asthma and other respiratory diseases based on haplotype association in MLK1 protein kinase gene
INVENTOR(S): Hakonarson, Hakon; Gurney, Mark E.; Halapi, Eva
PATENT ASSIGNEE(S): Iceland
SOURCE: U.S. Pat. Appl. Publ., 308pp., Cont.-in-part of Appl. No. PCT/US2006/003220.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20080146540	A1	20080619	US 2007-881406	20070726
WO 2005007144	A2	20050127	WO 2004-US22446	20040714
WO 2005007144	A3	20050616		
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 20060014165	A1	20060119	US 2005-43752	20050126
WO 2006081555	A2	20060803	WO 2006-US3220	20060126
WO 2006081555	A3	20070809		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				

PRIORITY APPLN. INFO.:		
US 2003-487072P	P	20030714
US 2004-559611P	P	20040405
WO 2004-US22446	A2	20040714
US 2005-43752	A1	20050126
WO 2006-US3220	A2	20060126

OTHER SOURCE(S): MARPAT 149:76598
AB Methods for diagnosis of asthma or a susceptibility to asthma are provided based on detection of at-risk haplotypes associated with the gene encoding mitogen-activated protein kinase MAP3K9 (also known as mixed lineage kinase 1, MLK1) located on human chromosome 14q24.2. Microsatellite and

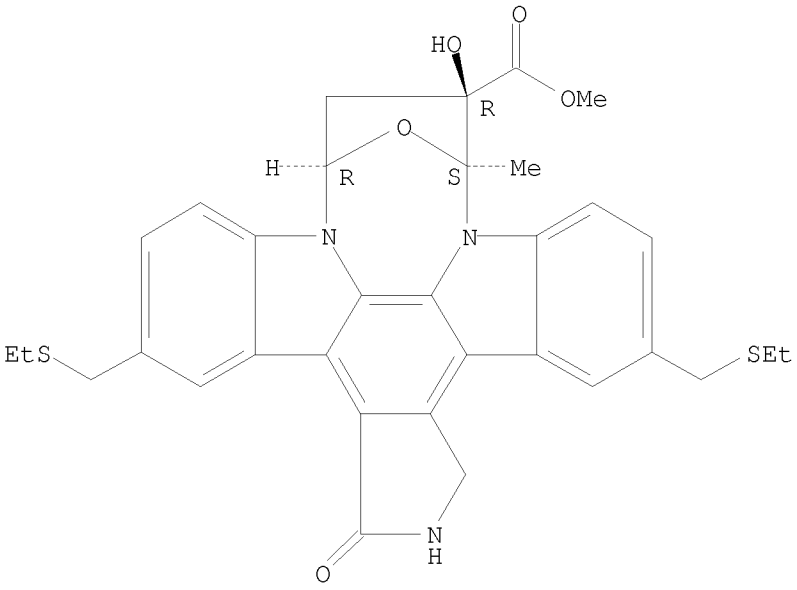
single nucleotide polymorphism (SNP) markers are provided, as are primers and amplimer sequences. Methods for treatment of asthma or a susceptibility to asthma based on detection of at-risk haplotypes associated with MAP3K9 are also disclosed. In particular, pathway targeting for treating individuals who are at-risk of developing asthma are described. In certain aspects, MLK1 inhibitors are used in treatment methods, including CEP-1347 and other indolocarbazole derivs.

IT 156177-65-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods of diagnosis and treatment for asthma and other respiratory diseases based on haplotype association in MLK1 protein kinase gene)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 5 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:640990 CAPLUS
DOCUMENT NUMBER: 149:24933
TITLE: Modulators of PAK-FMRP interaction for treatment of fragile X syndrome and methods for drug screening
INVENTOR(S): Tonegawa, Susumu; Hayashi, Mansuo; Dolan, Bridget
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA
SOURCE: PCT Int. Appl., 178pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008063933	A2	20080529	WO 2007-US84325	20071109
WO 2008063933	A3	20090319		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

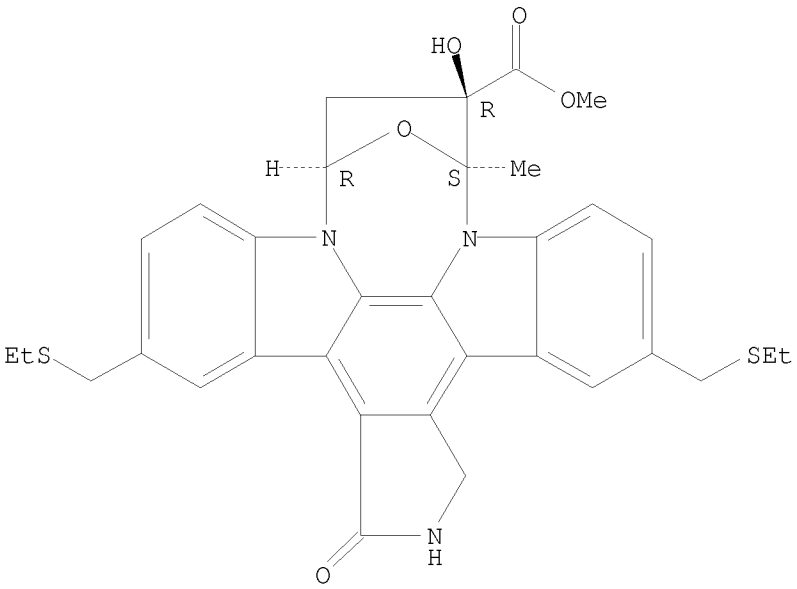
PRIORITY APPLN. INFO.: US 2006-858108P P 20061110

AB The present invention provides methods for treating fragile X syndrome and/or other neurodevelopmental disorders by administering p21 -activated kinase (PAK) modulators to a patient suffering from, susceptible to, and/or exhibiting one or more symptoms of FXS and/or other neurodevelopmental disorders. The present invention provides PAK modulators and pharmaceutical compns. comprising PAK modulators. The present invention further provides methods for identifying and/or characterizing PAK modulators. Thus, abnormalities in cortical spine morphol. of FXS patients and FMR1 knockout mice were opposite to those found in transgenic mice in which PAK activity was inhibited by its dominant neg. form. PAK was shown to bind to the product of the FMR1 gene, FMRP (fragile X mental retardation protein). The signaling pathways mediated by PAK and FMRP may therefore antagonize each other to regulate synaptic morphol. and/or function.

IT 156177-65-0, CEP 1347
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modulators of PAK-FMRP interaction for treatment of fragile X syndrome and methods for drug screening)

RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.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L4 ANSWER 6 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:253400 CAPLUS
DOCUMENT NUMBER: 148:276773
TITLE: Promotion of CNS axon regeneration by inhibition of JNK kinase signaling, and use for treatment of CNS diseases
INVENTOR(S): He, Zhigang; Yiu, Glenn
PATENT ASSIGNEE(S): Children's Medical Center Corporation, USA
SOURCE: PCT Int. Appl., 24pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008024776	A1	20080228	WO 2007-US76423	20070821
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20080051319	A1	20080228	US 2007-842542	20070821

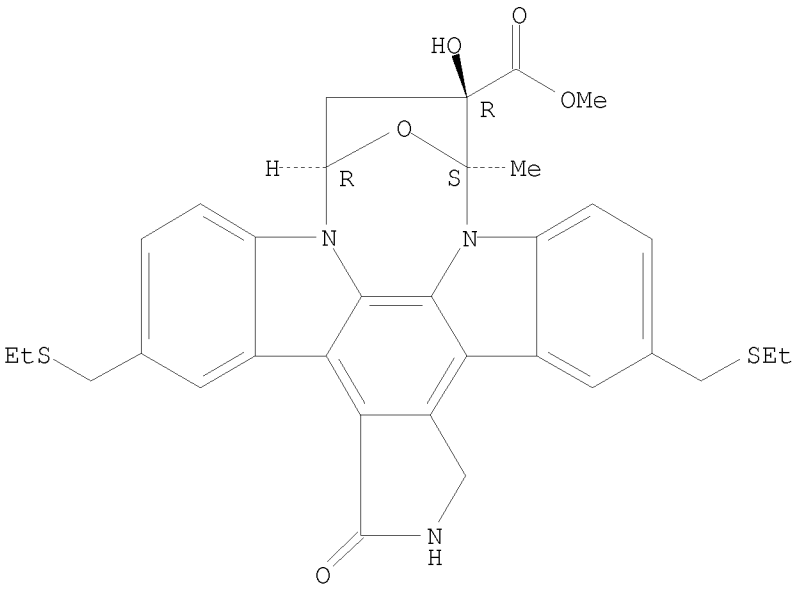
PRIORITY APPLN. INFO.: US 2006-839595P P 20060822

AB Regeneration of a lesioned CNS axon of a mature neuron, determined to be subject to regeneration inhibition by endogenous cJun-N-terminal kinase (JNK), is promoted by contacting the neuron with an exogenous JNK inhibitor at a concentration sufficient to partially inhibit the JNK, and thereby promote a resultant regeneration of the axon. In particular, it is shown that inhibition of JNK by a specific pharmacol. inhibitor, SP600125, blocks outgrowth inhibition by CNS myelin. Partial inhibition of JNK activation promotes axonal regeneration after spinal injury in rats. Improved neurol. outcome of spinal cord injury was demonstrated. JNK inhibition also promoted neural regeneration in animal models of focal brain ischemia.

IT 156177-65-0, CEP-1347
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(JNK inhibitor; promotion of CNS axon regeneration by inhibition of JNK kinase signaling, and use for treatment of CNS diseases)

RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:730759 CAPLUS
DOCUMENT NUMBER: 147:134456
TITLE: Treatment of HIV-1-associated dementia using inhibitors of glycogen synthase kinase (gsk)-3
INVENTOR(S): Gelbard, Harris A.; Maggirwar, Sanjay B.; Dewhurst, Stephen; Schifitto, Giovanni
PATENT ASSIGNEE(S): University of Rochester, USA
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007076372	A2	20070705	WO 2006-US62329	20061219
WO 2007076372	A3	20071101		
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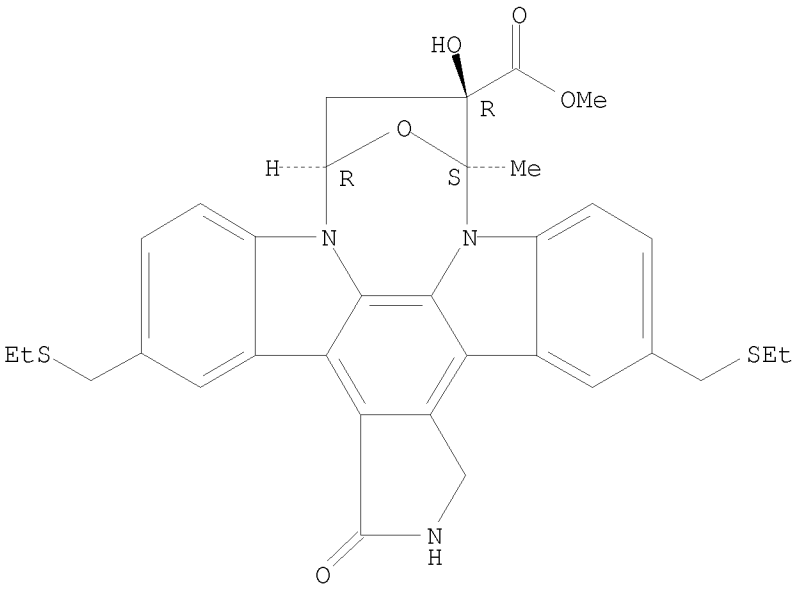
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
CA 2634932	A1	20070705	CA 2006-2634932	20061219
EP 1976976	A2	20081008	EP 2006-846697	20061219
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
US 20090081318	A1	20090326	US 2008-158896	20081029
PRIORITY APPLN. INFO.:			US 2005-753614P	P 20051223
			WO 2006-US62329	W 20061219

AB The invention provides a method for treating or preventing neurol. disease in a subject in need of such treatment or prevention, comprising administering to the subject a therapeutically ED of a GSK-3 inhibitor.

IT 156177-65-0, CEP 1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glycogen synthase kinase 3 inhibitors for treatment of HIV-1-associated dementia, and use with other agents)

RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.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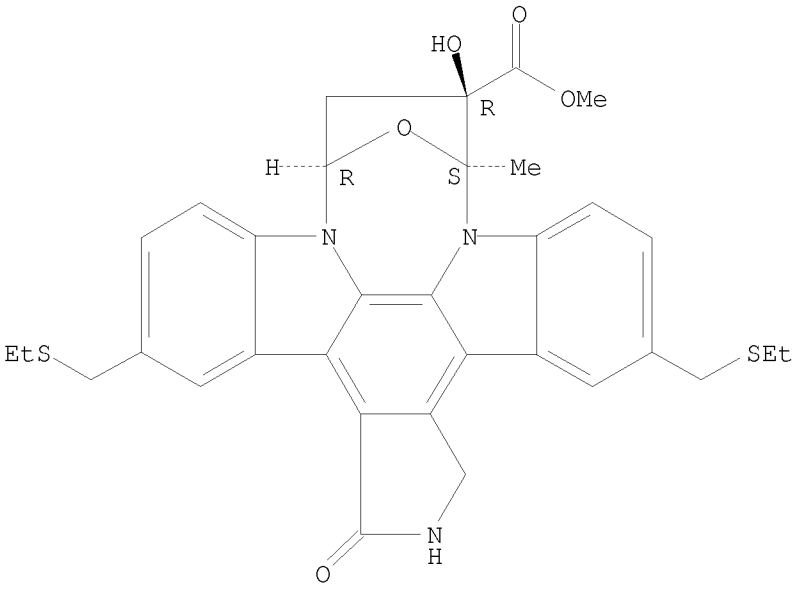
L4 ANSWER 8 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:644446 CAPLUS
DOCUMENT NUMBER: 147:64493
TITLE: Host proteins interacting with human immunodeficiency virus-1 and their use as targets for the treatment of AIDS
INVENTOR(S): Nguyen, Deborah; Kuhen, Kelli; Caldwell, Jeremy
PATENT ASSIGNEE(S): IRM LLC, Bermuda
SOURCE: PCT Int. Appl., 39pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007067737	A2	20070614	WO 2006-US46866	20061208
WO 2007067737	A3	20080327		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
AU 2006321848	A1	20070614	AU 2006-321848	20061208
CA 2629822	A1	20070614	CA 2006-2629822	20061208
EP 1957975	A2	20080820	EP 2006-848507	20061208
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				
JP 2009518042	T	20090507	JP 2008-544531	20061208
IN 2008DN04589	A	20080815	IN 2008-DN4589	20080528
CN 101317091	A	20081203	CN 2006-80044648	20080529
KR 2008080984	A	20080905	KR 2008-713695	20080605
MX 2008007345	A	20080623	MX 2008-7345	20080606
PRIORITY APPLN. INFO.:			US 2005-748759P P	20051208
			WO 2006-US46866 W	20061208

AB Host proteins interacting with human immunodeficiency virus 1 and that may be useful as drug targets for the treatment of AIDS are identified. These targets were identified by three different screens for protein interactions. The invention also provides methods of using the HIV-interacting host factors to screen for compds. that inhibit HIV infection. The methods comprise first screening test compds. for modulators of an HIV-interacting host factor disclosed herein, and then further screening the identified modulating compds. for ability to inhibit HIV infection. The invention further provides methods and pharmaceutical compns. for treating diseases and conditions associated with HIV infection.
IT 156177-65-0, CEP 1347
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as inhibitor of MLK3 in AIDS treatment; host proteins interacting with

HIV-1 and their use as targets for treatment of AIDS)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 9 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:561763 CAPLUS
DOCUMENT NUMBER: 146:494108
TITLE: Anti-angiogenic activity of 2-methoxyestradiol in combination with anti-cancer agents
INVENTOR(S): Plum, Stacy M.; Strawn, Steven J.; Lavallee, Theresa M.; Sidor, Carolyn F.; Fogler, William E.; Treston, Anthony M.
PATENT ASSIGNEE(S): Entremed, Inc., USA
SOURCE: PCT Int. Appl., 49pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007059111	A2	20070524	WO 2006-US44152	20061114
WO 2007059111	A3	20090514		
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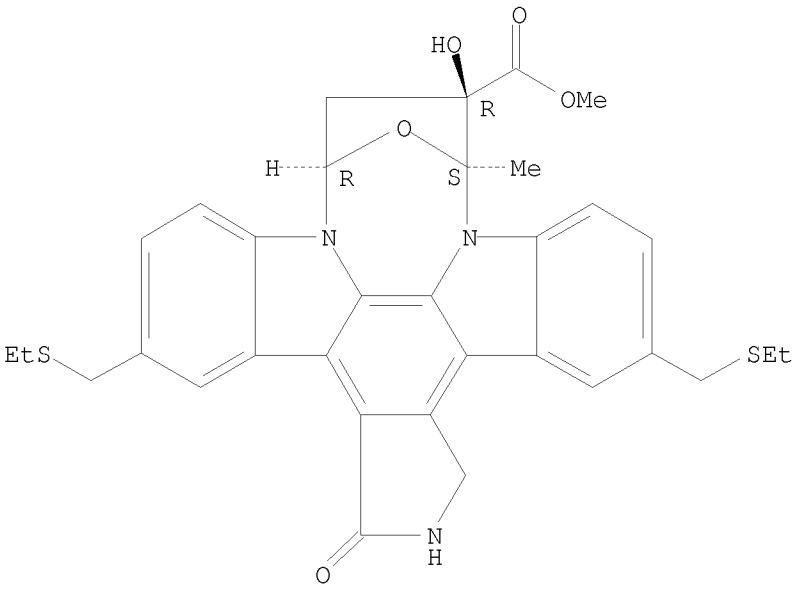
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
US 20070185069	A1	20070809	US 2006-599997	20061114
PRIORITY APPLN. INFO.:			US 2005-736220P P	20051114
			US 2006-788354P P	20060331

AB The present invention relates generally to methods and compns. of treating disease characterized by abnormal cell proliferation and/or abnormal or undesirable angiogenesis by administering antiangiogenic agents in combination with chemotherapeutic agents. More specifically, the present invention relates to a methods and compns. of treating diseases characterized by abnormal cell proliferation and/or abnormal or undesirable angiogenesis by administering 2-methoxyestradiol, in combination with chemotherapeutic agents.

IT 156177-65-0, CEP-1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-angiogenic activity of 2-methoxyestradiol and other estradiols in combination with anti-cancer agents)

RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.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L4 ANSWER 10 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:150806 CAPLUS
DOCUMENT NUMBER: 146:229498
TITLE: Targeting TNF-α converting enzyme (TACE)-dependent growth factor shedding in cancer therapy
INVENTOR(S): Kenny, Paraic A.; Bissell, Mina J.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007016597	A2	20070208	WO 2006-US30008	20060731
WO 2007016597	A3	20071108		

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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

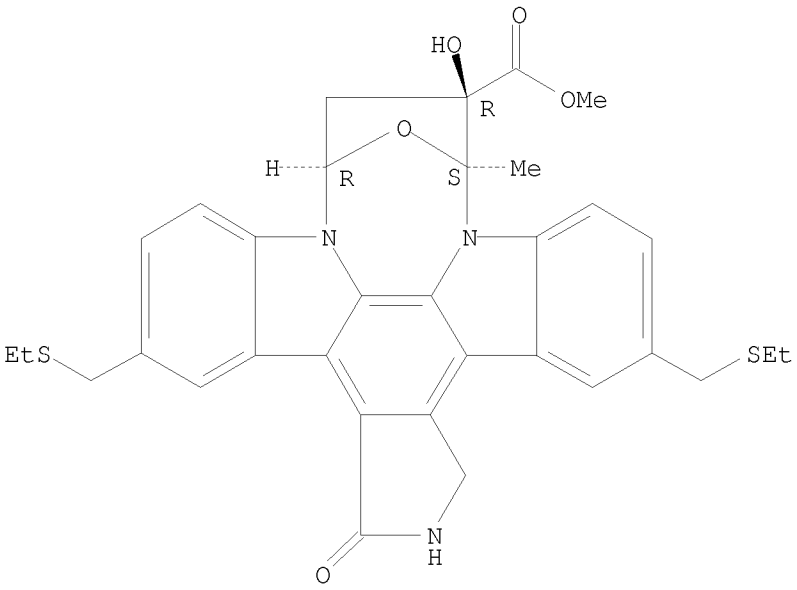
PRIORITY APPLN. INFO.: US 2005-703654P P 20050729

AB The invention provides methods for modulating tumor cell proliferation by contacting cells (e.g. tumor cells) with a TACE inhibitor and a compound that inhibits EGFR tyrosine kinase, whereby the TACE inhibitor enhances the sensitivity of the cell to the EGFR tyrosine kinase inhibitor. Addnl., methods for treating cancer and methods for identifying TACE inhibitors is also provided.

IT 156177-65-0, CEP-1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting TNF-α converting enzyme (TACE)-dependent growth factor shedding in cancer therapy)

RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.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L4 ANSWER 11 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:769183 CAPLUS
DOCUMENT NUMBER: 145:181019
TITLE: Use of inhibitors of jun N-terminal kinases to treat glaucoma
INVENTOR(S): Fleenor, Debra L.; Pang, Iok-Hou
PATENT ASSIGNEE(S): Alcon, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont.-in-part of U.S. Ser. No. 259,566.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20060172991	A1	20060803	US 2006-394893	20060331
US 20060094753	A1	20060504	US 2005-259566	20051026
AU 2005302511	A1	20060511	AU 2005-302511	20051027
CA 2582316	A1	20060511	CA 2005-2582316	20051027
EP 1804790	A2	20070711	EP 2005-824291	20051027
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CN 101048156	A	20071003	CN 2005-80036654	20051027
JP 2008518922	T	20080605	JP 2007-539134	20051027
AU 2007235111	A1	20071018	AU 2007-235111	20070314
CA 2644721	A1	20071018	CA 2007-2644721	20070314
WO 2007117849	A2	20071018	WO 2007-US63961	20070314
WO 2007117849	A3	20080410		
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EP 2004158	A2	20081224	EP 2007-758510	20070314
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MX 2007004264	A	20070615	MX 2007-4264	20070411
KR 2007070208	A	20070703	KR 2007-710587	20070510
MX 2008011319	A	20080919	MX 2008-11319	20080904
CN 101415407	A	20090422	CN 2007-80011692	20080928
KR 2008108503	A	20081215	KR 2008-723895	20080930

PRIORITY APPLN. INFO.:	US 2004-623755P	P	20041029
	US 2005-259566	A2	20051026
	WO 2005-US38825	W	20051027
	US 2006-394893	A	20060331
	WO 2007-US63961	W	20070314

AB Compns. and methods for lowering intraocular pressure (IOP) and/or

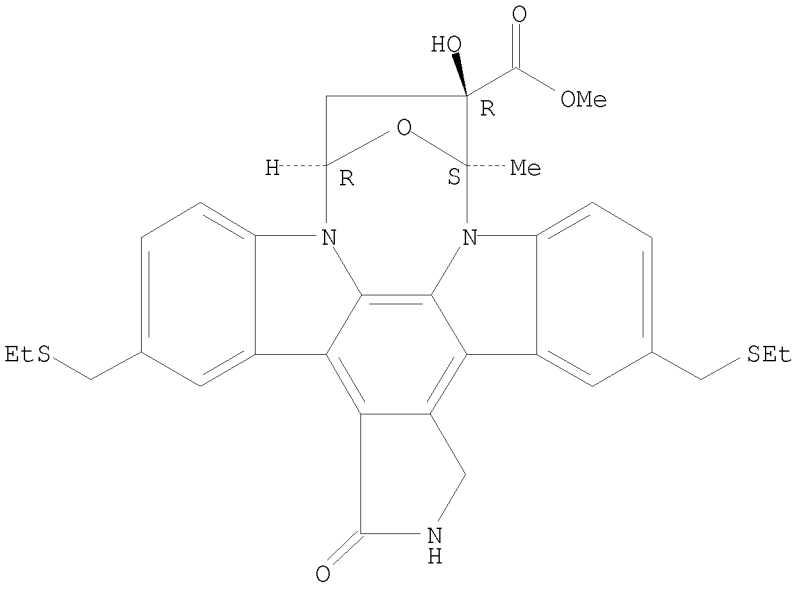
providing neuroprotection are disclosed. The compns. and methods are particularly directed to the use inhibitors of Jun N-terminal kinases (JNK) to lower IOP and/or provide neuroprotection.

IT 156177-65-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(JNK kinase inhibitors for treatment of glaucoma)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 12 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:51211 CAPLUS
DOCUMENT NUMBER: 144:148372
TITLE: Methods of diagnosis and treatment for asthma and other respiratory diseases based on haplotype association in MLK1 protein kinase gene
INVENTOR(S): Hakonarson, Hakon; Gurney, Mark E.; Halapi, Eva
PATENT ASSIGNEE(S): Decode Genetics Ehf., Iceland
SOURCE: U.S. Pat. Appl. Publ., 1224 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20060014165	A1	20060119	US 2005-43752	20050126
WO 2005007144	A2	20050127	WO 2004-US22446	20040714
WO 2005007144	A3	20050616		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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CA 2595875	A1	20060803	CA 2006-2595875	20060126
WO 2006081555	A2	20060803	WO 2006-US3220	20060126
WO 2006081555	A3	20070809		
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EP 1848436	A2	20071031	EP 2006-734053	20060126
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US 20080146540	A1	20080619	US 2007-881406	20070726

PRIORITY APPLN. INFO.:		
US 2003-487072P	P	20030714
US 2004-559611P	P	20040405
WO 2004-US22446	A2	20040714
US 2005-43752	A	20050126
WO 2006-US3220	W	20060126

OTHER SOURCE(S): MARPAT 144:148372

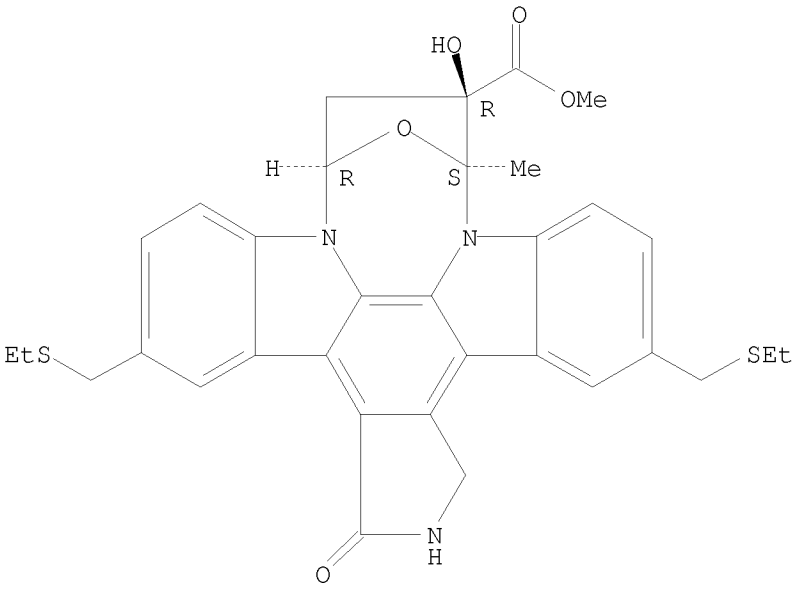
AB Methods for diagnosis of asthma or a susceptibility to asthma are provided based on detection of at-risk haplotypes associated with the gene encoding mitogen-activated protein kinase MAP3K9 (also known as mixed lineage kinase 1, MLK1) located on human chromosome 14q24.2. Microsatellite and single nucleotide polymorphism (SNP) markers are provided, as are primers and amplimer sequences. Methods for treatment of asthma or a susceptibility to asthma based on detection of at-risk haplotypes associated with MAP3K9 are also disclosed. In particular, pathway targeting for treating individuals who are at-risk of developing asthma are described. In certain aspects, MLK1 inhibitors are used in treatment methods, including CEP-1347 and other indolocarbazole derivs.

IT 156177-65-0, CEP-1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods of diagnosis and treatment for asthma and other respiratory diseases based on haplotype association in MLK1 protein kinase gene)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 13 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:1118416 CAPLUS
DOCUMENT NUMBER: 144:141668
TITLE: Treatment of Parkinson's disease: what' on the horizon?
AUTHOR(S): Wu, Stacy S.; Frucht, Steven J.
CORPORATE SOURCE: Department of Neurology, University Hospital of Basel, Basel, Switz.
SOURCE: CNS Drugs (2005), 19(9), 723-743
CODEN: CNDREF; ISSN: 1172-7047
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Few neurol. diseases have received as much attention and investment in research as Parkinson's disease. Although great strides have been made in the development of agents to treat this neurodegenerative disease, none yet address the underlying problem associated with it, the progressive loss of dopaminergic neurons. Current therapeutic strategies for Parkinson's disease focus primarily on reducing the severity of its symptoms using dopaminergic medications. Although providing substantial benefit, these agents are burdened by adverse effects and long-term complications. This review highlights new and emerging therapies for Parkinson's disease, categorised as symptomatic, neuroprotective and neurorestorative, although at times, this distinction is not easily made. Novel symptomatic treatments target nondopaminergic areas in the hope of avoiding the motor complications seen with dopaminergic therapies. Two emerging treatment approaches under investigation are adenosine A2A receptor antagonists (such as istradefylline [KW-6002]) and glutamate AMPA receptor antagonists (such as talampanel [LY-300164]). In 2003, the results from two studies using istradefylline in patients with Parkinson's disease were published, with both showing a pos. benefit of the study drug when used as adjunctive therapy to levodopa. In non-human primate models of Parkinson's disease, talampanel has been found to have antiparkinsonian effects when administered as high-dose monotherapy and antidyskinetic effects on levodopa-induced dyskinesias. NS-2330, another drug currently undergoing clin. trials, is a triple monoamine reuptake inhibitor that has therapeutic potential in both Parkinson's and Alzheimer's disease. A phase II proof-of-concept study is currently underway in early Parkinson's disease. However, a recently published study in advanced Parkinson's disease showed no therapeutic benefit of NS-2330 in this patient population. Even more exciting are agents that have a neuroprotective or neurorestorative role. These therapies aim to prevent disease progression by targeting the mechanisms involved in the pathogenesis of Parkinson's disease. Several lines of investigation for neuroprotective therapies have been taken, including the antioxidant coenzyme Q10 (ubidecarenone) and anti-apoptotic agents such as CEP-1347. Studies in patients with Parkinson's disease with coenzyme Q10 have suggested that it slows down functional decline. The PRECEPT study is currently in progress to assess the neuroprotective role of CEP-1347 in the early phase of the disease. Gene therapy is another exciting arena and includes both potentially neuroprotective and neurorestorative agents. Novel methods include subthalamic glutamic acid decarboxylase gene therapy and the use of glial cell line-derived neurotrophic factor (GDNF). Eleven of 12 patients have been enrolled in the first FDA-approved phase I subthalamic glutamic acid decarboxylase gene therapy trial for Parkinson's disease, with currently no evidence of adverse events. GDNF delivered intracerebroventricularly

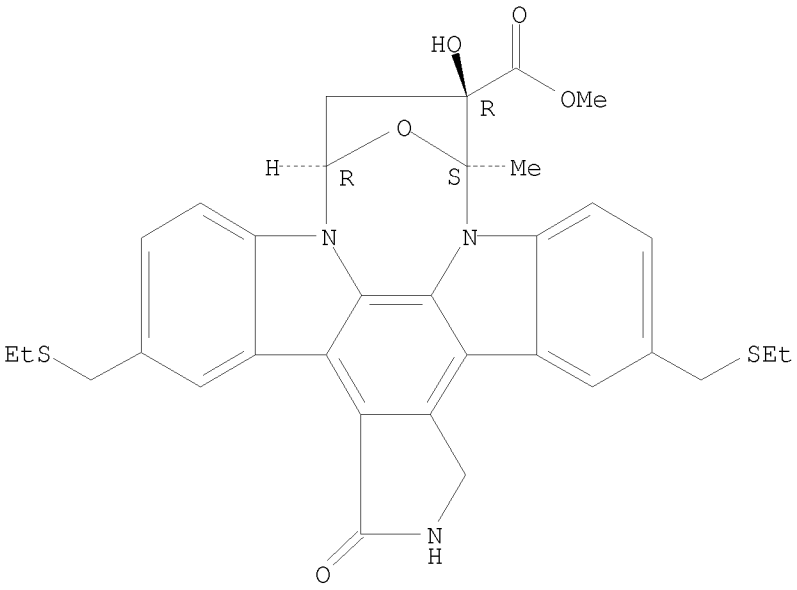
was studied in a small population of patients with Parkinson's disease, but unfortunately did not reveal pos. results. Other methods of administering GDNF include direct delivery via infusions into the basal ganglia and the use of viral vectors; thus far, these approaches have shown promising results. This is an exciting and rewarding time for research into Parkinson's disease. With so many therapies currently under investigation, the time is ripe for the beginning of a new phase of treatment strategies.

IT 156177-65-0, CEP-1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotective and neurorestorative strategies involving use of anti-apoptotic agent CEP-1347 may prove to be useful therapeutic option for treatment of Parkinson's disease in human)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 130 THERE ARE 130 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:1028090 CAPLUS
DOCUMENT NUMBER: 143:299099
TITLE: Mixed lineage kinases as drug targets for the control of cell proliferation in the treatment of proliferative disease
INVENTOR(S): Shapiro, Paul S.
PATENT ASSIGNEE(S): University of Maryland, Baltimore, USA
SOURCE: U.S. Pat. Appl. Publ., 33 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20050209299	A1	20050922	US 2005-81929	20050315
CA 2557869	A1	20051013	CA 2005-2557869	20050316
WO 2005094802	A2	20051013	WO 2005-US8682	20050316
WO 2005094802	A3	20070531		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, AP, EA, EP, OA				
EP 1727528	A2	20061206	EP 2005-760393	20050316
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU				
JP 2007529540	T	20071025	JP 2007-504050	20050316
MX 2006010490	A	20061208	MX 2006-10490	20060914

PRIORITY APPLN. INFO.:	US 2004-553497P	P	20040316
	US 2005-81929	A	20050315
	WO 2005-US8682	W	20050316

AB Provided herein are methods of using an inhibitor of a mixed lineage kinase to inhibit cell proliferation in neoplastic cells. Such methods may be used to treat a cancer and further may be used in conjunction with administration of an anticancer drug at a reduced dosage to treat a cancer with a concomitant reduction in toxicity to an individual receiving the treatment. Also provided is a method to screen for inhibitory agents to inhibit an activity of a MLK protein or polypeptide and to inhibit cell proliferation of a neoplastic cell having the MLK activity. Use of the drug CEP-11004 to specifically inhibit mixed lineage kinase 3 (MLK3 kinase) in HeLa cells is demonstrated. Inhibition of MLK3 was specific and inhibited cell proliferation with cells accumulating in G2 or M phases. The inhibition could be overcome by overexpression of the MLK3 gene.

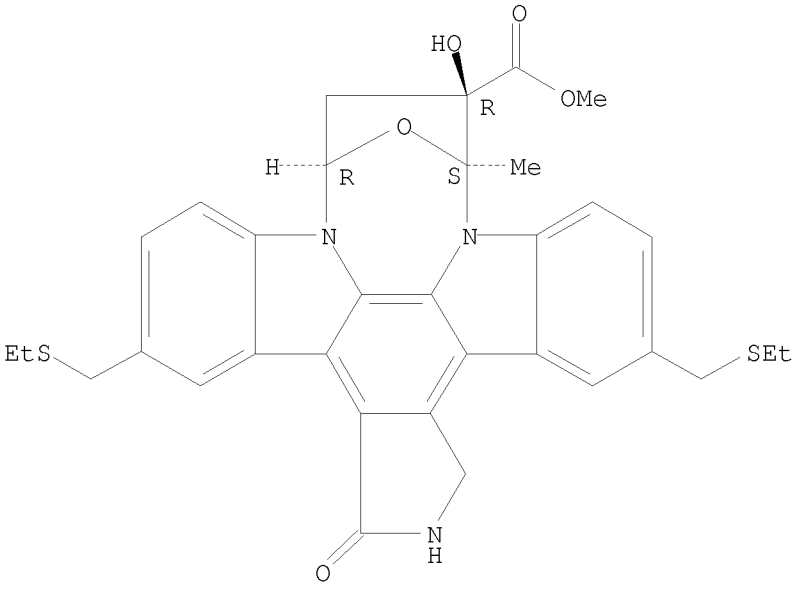
IT 156177-65-0
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(as inhibitor of mixed lineage kinases; mixed lineage kinases as drug targets for control of cell proliferation in treatment of proliferative disease)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

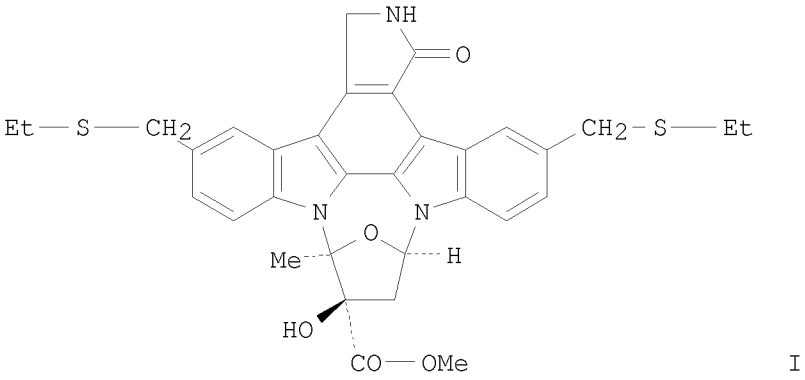
Absolute stereochemistry.



L4 ANSWER 15 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:984071 CAPLUS
DOCUMENT NUMBER: 143:292453
TITLE: Crystalline forms of an 9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylate pharmaceutical
INVENTOR(S): Rock, Michael Harold; Lopez de Diego, Heidi; Christensen, Kim Lasse; Nielsen, Ole; Buur, Anders; Howells, Mark
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2005082920	A1	20050909	WO 2005-DK127		20050224
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
AU 2005217024	A1	20050909	AU 2005-217024		20050224
CA 2557371	A1	20050909	CA 2005-2557371		20050224
EP 1720891	A1	20061115	EP 2005-706789		20050224
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU					
CN 1922196	A	20070228	CN 2005-80005979		20050224
BR 2005007995	A	20070731	BR 2005-7995		20050224
JP 2007523915	T	20070823	JP 2007-500051		20050224
ZA 2006006556	A	20080227	ZA 2006-6556		20050224
MX 2006009148	A	20061002	MX 2006-9148		20060811
KR 2007012644	A	20070126	KR 2006-717263		20060825
IN 2006CN03095	A	20070608	IN 2006-CN3095		20060825
US 20070191339	A1	20070816	US 2006-597977		20060912
NO 2006004348	A	20060926	NO 2006-4348		20060926
PRIORITY APPLN. INFO.:			DK 2004-326	A	20040227
			US 2004-548351P	P	20040227
			WO 2005-DK127	W	20050224

GI



I

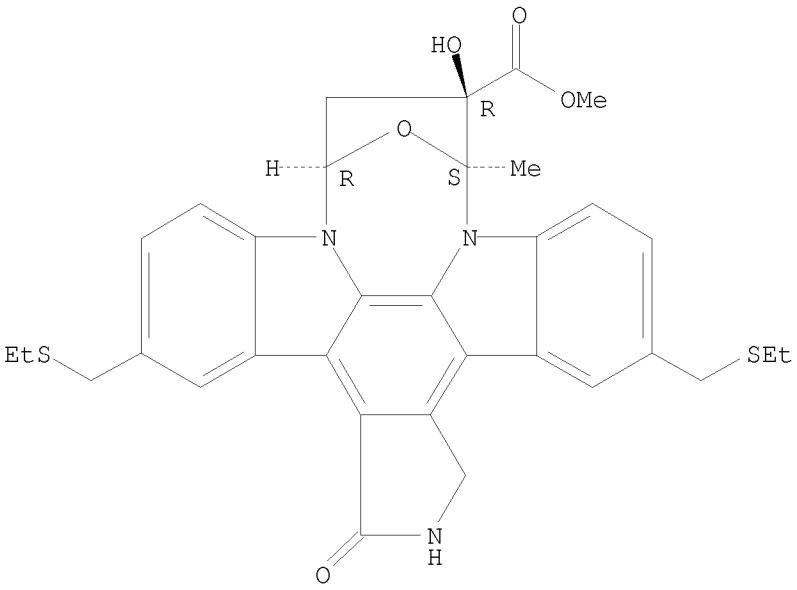
AB Described are crystalline forms of the pharmaceutical compound [9S-(9α,10β,12α)]-5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12- hexahydro-10-hydroxy-9-methyl-1-oxo-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid Me ester (I), as well as methods for their use and preparation A crystalline γ-form of I was prepared from aa solution of I in acetone with K2CO3. XRPD data are given.

IT 156177-65-0
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(crystalline forms of an 9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylate pharmaceutical)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

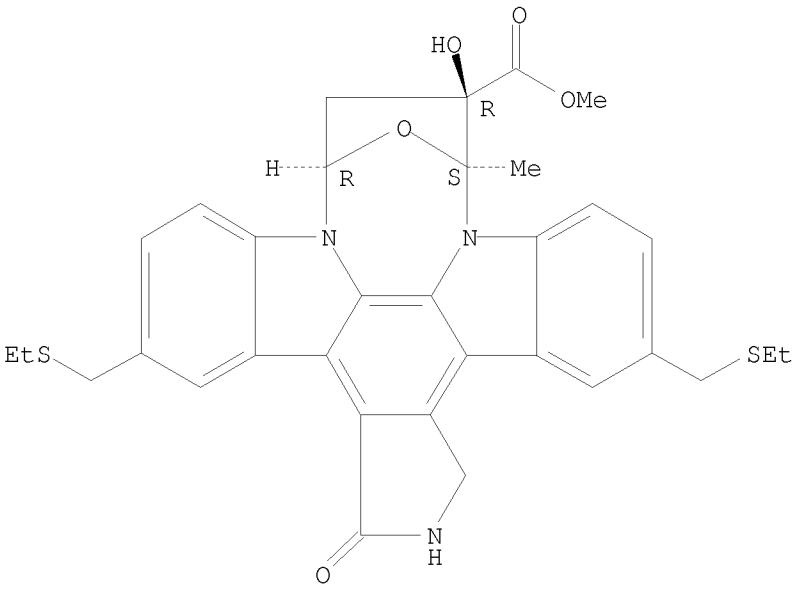
Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:273346 CAPLUS
DOCUMENT NUMBER: 142:385441
TITLE: Inhibition of microglial inflammation by the MLK inhibitor CEP-1347
AUTHOR(S): Lund, Soren; Porzgen, Peter; Mortensen, Anne Louise; Hasseldam, Henrik; Bozyczko-Coyne, Donna; Morath, Siegfried; Hartung, Thomas; Bianchi, Marina; Ghezzi, Pietro; Bsibsi, Malika; Dijkstra, Sipke; Leist, Marcel
CORPORATE SOURCE: H. Lundbeck A/S, Valby, 2500, Den.
SOURCE: Journal of Neurochemistry (2005), 92(6), 1439-1451
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CEP-1347 is a potent inhibitor of the mixed lineage kinases (MLKs), a distinct family of mitogen-activated protein kinase kinase kinases (MAPKKK). It blocks the activation of the c-Jun/JNK apoptotic pathway in neurons exposed to various stressors and attenuates neurodegeneration in animal models of Parkinson's disease (PD). Microglial activation may involve kinase pathways controlled by MLKs and might contribute to the pathol. of neurodegenerative diseases. Therefore, the possibility that CEP-1347 modulates the microglial inflammatory response [tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocyte chemotactic protein-1 (MCP-1)] was explored. Indeed, the MLK inhibitor CEP-1347 reduced cytokine production in primary cultures of human and murine microglia, and in monocyte/macrophage-derived cell lines, stimulated with various endotoxins or the plaque forming peptide Aβ1-40. Moreover, CEP-1347 inhibited brain TNF production induced by intracerebroventricular injection of lipopolysaccharide in mice. As expected from a MLK inhibitor, CEP-1347 acted upstream of p38 and c-Jun activation in microglia by dampening the activity of both pathways. These data imply MLKs as important, yet unrecognized, modulators of microglial inflammation, and demonstrate a novel anti-inflammatory potential of CEP-1347.
IT 156177-65-0, CEP-1347
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of microglial inflammation by MLK inhibitor CEP-1347)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

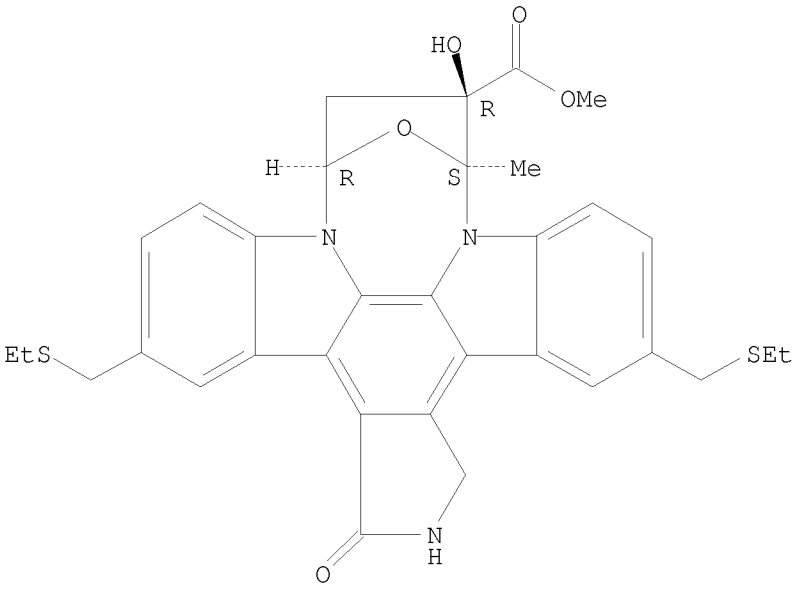
L4 ANSWER 17 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:207289 CAPLUS
DOCUMENT NUMBER: 142:309743
TITLE: Mixed-lineage kinase inhibitors require the activation of Trk receptors to maintain long-term neuronal trophism and survival
AUTHOR(S): Wang, Leo H.; Paden, Andrew J.; Johnson, Eugene M., Jr.
CORPORATE SOURCE: Departments of Neurology and Molecular Biology & Pharmacology, Washington University School of Medicine, St. Louis, MO, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2005), 312(3), 1007-1019
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Small-mol. mixed-lineage kinase (MLK) inhibitors, such as CEP-1347 [3,9-bis[(ethylthio)methyl]-(8R*,9S*,11S*)-(-)-9-hydroxy-9-methoxycarbonyl-8-methyl-2,3,9,10-tetrahydro-8,11-epoxy-1H,8H,11H-2,7b,11a-triazadibenzo(a,g)cycloocta(cde)trinden-1-one] and CEP-11004 [3,9-bis-[(isopropylthio)methyl]-(8R*,9S*,11S*)-(-)-9-hydroxy-9-methoxycarbonyl-8-methyl-2,3,9,10-tetrahydro-8,11-epoxy-1H,8H,11H-2,7b,11a-triazadibenzo(a,g)cycloocta(cde)trinden-1-one], prevent c-Jun NH2-terminal kinase (JNK) pathway activation as well as the consequent neuronal cell death in many cell culture and animal models. In the cell culture model of nerve growth factor (NGF)-deprived sympathetic neurons, we find that CEP-11004 induced a .apprx.3-fold increase in the mRNA and protein levels of TrkA, the NGF receptor. This resulted in ligand-independent activation of the TrkA receptor and the downstream phosphatidylinositol 3-kinase (PI3-kinase) pathway. Addition of the Trk inhibitor K252a [(8R*,9S*,11S*)-(-)-9-hydroxy-9-methoxycarbonyl-8-methyl-2,3,9,10-tetrahydro-8,11-epoxy-1H,8H,11H-2,7b,11a-triazadibenzo(a,g)cycloocta(cde)-trinden-1-one] or the PI3-kinase inhibitor LY294002 [2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one] significantly decreased the protein synthesis rates, mitochondrial function, and neuronal survival maintained by CEP-11004. In contrast to sympathetic neurons, MLK inhibitors maintain only short-term survival of potassium- and serum-deprived rat cerebellar granule neurons (CGNs), despite continuous inhibition of the JNK pathway. We found that similar to sympathetic neurons, CEP-11004 increased the levels of the Trk receptor expressed in CGNs, TrkB. However, CGNs required the addition of the exogenous ligand brain-derived neurotrophic factor (BDNF) to activate the PI3-kinase pathway and to maintain long-term survival. BDNF activated TrkB, but caused rapid down-regulation of activated receptors and maintained only minimal survival. Therefore, increase in TrkB levels by CEP-11004 mediated a synergism with BDNF resulting in long-term survival in response to the combined treatment of CEP-11004 and BDNF. Taken together, our studies suggest that in addition to the direct inhibition of the JNK pathway, the indirect activation of the PI3-kinase pathway via Trk activation is important for MLK inhibitor-mediated neuronal survival and trophism.

IT 156177-65-0, CEP-1347
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); BIOL (Biological study)
(mixed-lineage kinase inhibitors require the activation of Trk receptors to maintain long-term neuronal trophism and survival)

RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

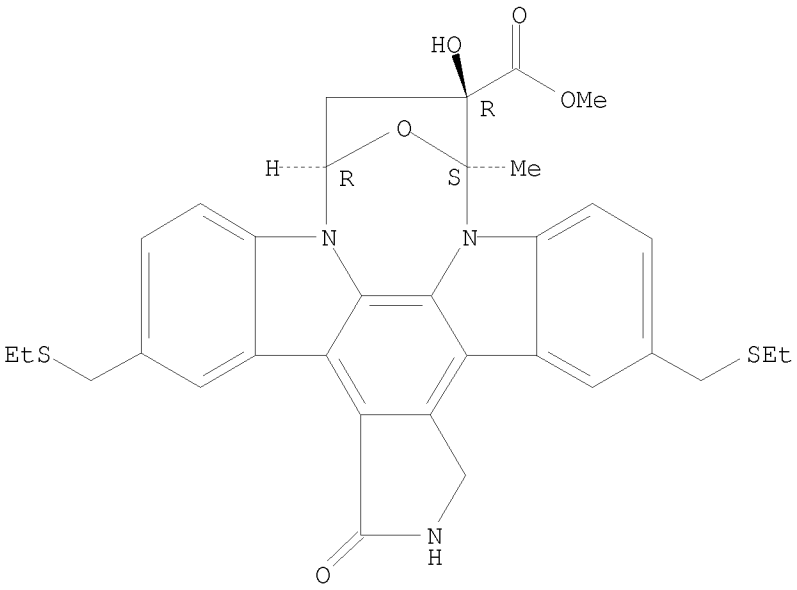
Absolute stereochemistry.



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:146539 CAPLUS
DOCUMENT NUMBER: 142:328799
TITLE: Targeting the JNK signaling pathway for stroke and Parkinson's diseases therapy
AUTHOR(S): Kuan, Chia-Yi; Burke, Robert E.
CORPORATE SOURCE: Division of Developmental Biology, Cincinnati Children's Hospital Research Foundation, Cincinnati, OH, 45229, USA
SOURCE: Current Drug Targets: CNS & Neurological Disorders (2005), 4(1), 63-67
CODEN: CDTCCC; ISSN: 1568-007X
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The c-Jun NH2-terminal Kinase (JNK) signaling pathway is frequently induced by cellular stress and correlated with neuronal death. This unique property makes JNK signaling a promising target for developing pharmacol. intervention. Among several neurol. disorders, JNK signaling is particularly implicated in ischemic stroke and Parkinson's disease. The inhibitors of the JNK signaling pathway include upstream kinase inhibitors (for example, CEP-1347), small chemical inhibitors of JNK (SP600125 and AS601245), and peptide inhibitors of the interaction between JNK and its substrates (D-JNKI and I-JIP). The mechanisms by which JNK signaling induces apoptosis and evidence of cytoprotective effects of these JNK inhibitors are summarized in the present review.
IT 156177-65-0, CEP-1347
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting the JNK signaling pathway for stroke and Parkinson's diseases therapy)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:71087 CAPLUS
DOCUMENT NUMBER: 142:183231
TITLE: Methods of diagnosis and treatment for asthma and other respiratory diseases based on haplotype association
INVENTOR(S): Hakonarson, Hakon; Gurney, Mark E.; Halapi, Eva
PATENT ASSIGNEE(S): Decode Genetics Ehf., Iceland
SOURCE: PCT Int. Appl., 640 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005007144	A2	20050127	WO 2004-US22446	20040714
WO 2005007144	A3	20050616		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004257748	A1	20050127	AU 2004-257748	20040714
AU 2004257748	B2	20081030		
CA 2532203	A1	20050127	CA 2004-2532203	20040714
EP 1646372	A2	20060419	EP 2004-778119	20040714
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
US 20060014165	A1	20060119	US 2005-43752	20050126
MX 2006000514	A	20060620	MX 2006-514	20060112
US 20080146540	A1	20080619	US 2007-881406	20070726

PRIORITY APPLN. INFO.:

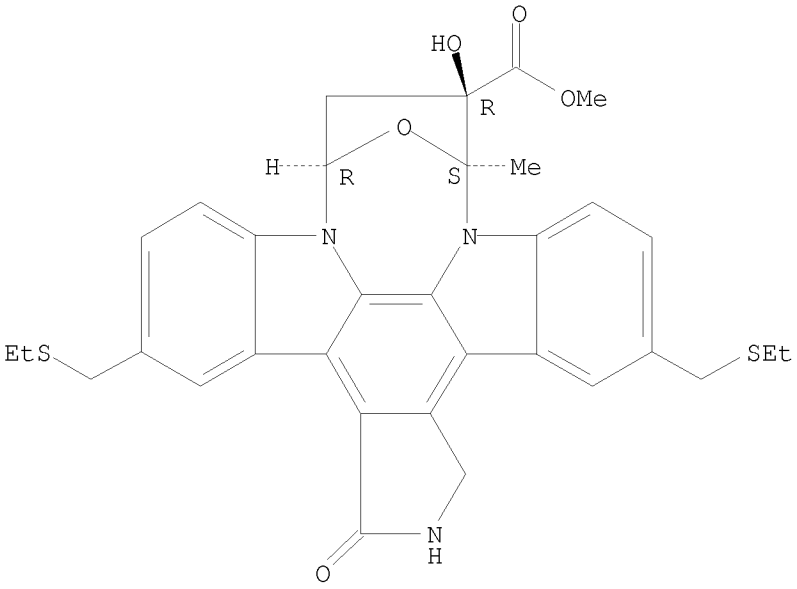
US 2003-487072P	P	20030714
US 2004-559611P	P	20040405
WO 2004-US22446	W	20040714
US 2005-43752	A1	20050126
WO 2006-US3220	A2	20060126

OTHER SOURCE(S): MARPAT 142:183231

AB Methods for diagnosis of asthma or a susceptibility to asthma based on detection of at-risk haplotypes associated with the human mitogen-activated protein kinase kinase kinase 9 gene (MAP3K9, also known as MLK1 or asthma sensitivity gene AS1) located on chromosome 14q24.2-3 are disclosed. Also methods for treatment of asthma or a susceptibility to asthma based on detection of at-risk haplotypes associated with MAP3K9 are disclosed. In particular, pathway targeting for treating individuals who are at-risk of developing asthma are described. A large number of single nucleotide polymorphisms (SNPs), microsatellite polymorphisms, and sequence tagged site polymorphisms of the MAP3K9 gene are provided. Indolocarbazole derivative analogs of CEP-1347 or K-252a are provided as MLK1 inhibitors for use in treatment methods.

IT 156177-65-0D, CEP 1347, analogs
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diagnosis and treatment for asthma and other respiratory diseases based on haplotype association)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

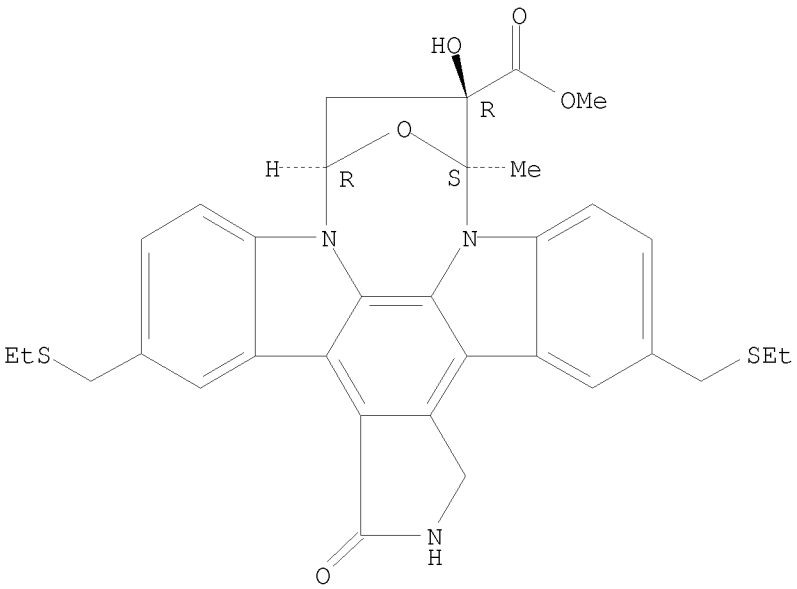
L4 ANSWER 20 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:824059 CAPLUS
DOCUMENT NUMBER: 141:307497
TITLE: Use of caspase inhibitors as antiviral agents, and test system for their discovery
INVENTOR(S): Ludwig, Stefan; Planz, Oliver; Sedlacek, Hans-Harald; Pleschka, Stephan
PATENT ASSIGNEE(S): Medinnova Gesellschaft fur Medizinische Innovationen aus Akademischer Forschung m.b.H., Germany
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004085682	A2	20041007	WO 2004-DE646	20040324
WO 2004085682	A3	20050331		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10313636	A1	20041014	DE 2003-10313636	20030326
EP 1617858	A2	20060125	EP 2004-722803	20040324
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK				
JP 2006524640	T	20061102	JP 2006-504277	20040324
US 20070172489	A1	20070726	US 2006-550856	20060710
US 20090155270	A1	20090618	US 2008-331864	20081210

PRIORITY APPLN. INFO.:		
DE 2003-10313636	A	20030326
WO 2004-DE646	W	20040324
US 2006-550856	B1	20060710

AB The invention discloses the use of at least one caspase inhibitor, especially a caspase 3 inhibitor, for producing a pharmaceutical composition for the prophylaxis and/or treatment of a viral infection, especially an infection with an neg.-strand RNA virus, preferably an influenza infection. The invention also relates to a test system for identifying such inhibitors.
IT 156177-65-0, CEP-1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(caspase inhibitors as antiviral agents, and test system for discovery thereof)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

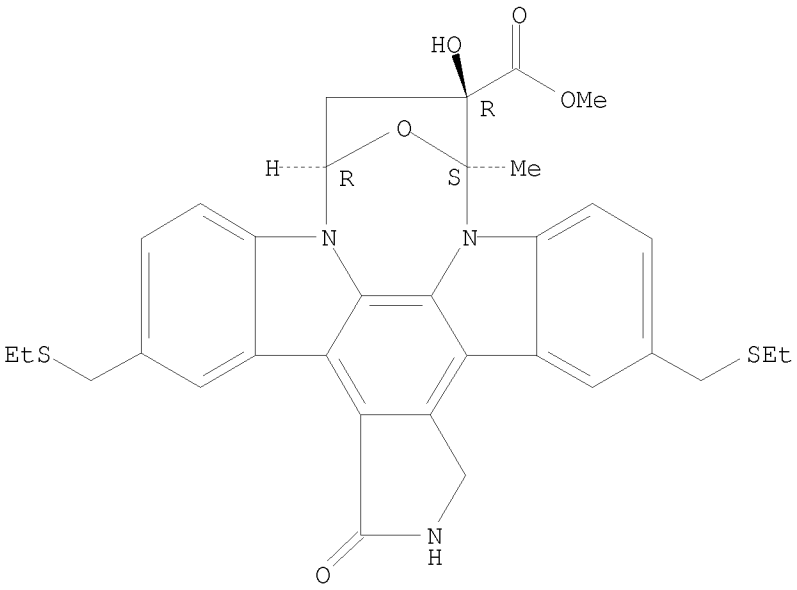
Absolute stereochemistry.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 21 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:791789 CAPLUS
DOCUMENT NUMBER: 142:309272
TITLE: A clue to the therapy of neurofibromatosis type 2: NF2/merlin is a PAK1 inhibitor
AUTHOR(S): Hirokawa, Yumiko; Tikoo, Anjali; Huynh, John; Utermark, Tamara; Hanemann, C. Oliver; Giovannini, Marco; Xiao, Guang-Hui; Testa, Joseph R.; Wood, John; Maruta, Hiroshi
CORPORATE SOURCE: Ludwig Institute for Cancer Research, Melbourne, Australia
SOURCE: Cancer Journal (Sudbury, MA, United States) (2004), 10(1), 20-26
CODEN: CAJOCB; ISSN: 1528-9117
PUBLISHER: Jones and Bartlett Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB BACKGROUND Neurofibromatosis type 2 is a group of tumors caused by loss-of-function mutations of a tumor suppressor-gene encoding NF2/merlin. Development of chemotherapeutics for this disease, which often threatens the life of young children, has been hampered by a limited information on the signaling function of NF2. NF2 can inhibit Ras-induced malignant transformation. However, the primary (signaling) target of NF2 in the oncogenic pathway has not been previously identified. RESULTS Here, using a series of NF2 constructs, we show that NF2 inhibits directly the Rac/CDC42-dependent Ser/Thr kinase PAK1, which is essential for both Ras transformation and neurofibromatosis type 1 (NF1), through two sep. domains. A mutant of NF2, that lacks the PAK1-inhibiting domain of 78 amino acids (NF78C, residues 447-524), fails to suppress Ras transformation. Furthermore, PAK1-specific inhibitors CEP-1347 and WR-PAK18 selectively inhibit the growth of NF2 deficient cancer cells, but not NF2-pos. cells. CONCLUSIONS These results suggest that PAK1 is essential for the malignant growth of NF2-deficient cells, and that PAK1-blocking drugs could be potentially useful for the treatment of neurofibromatosis types 2, in addition to Ras-induced cancers and neurofibromatosis type 1.
IT 156177-65-0, CEP-1347
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapy of neurofibromatosis type 2: NF2/merlin is PAK1 inhibitor)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

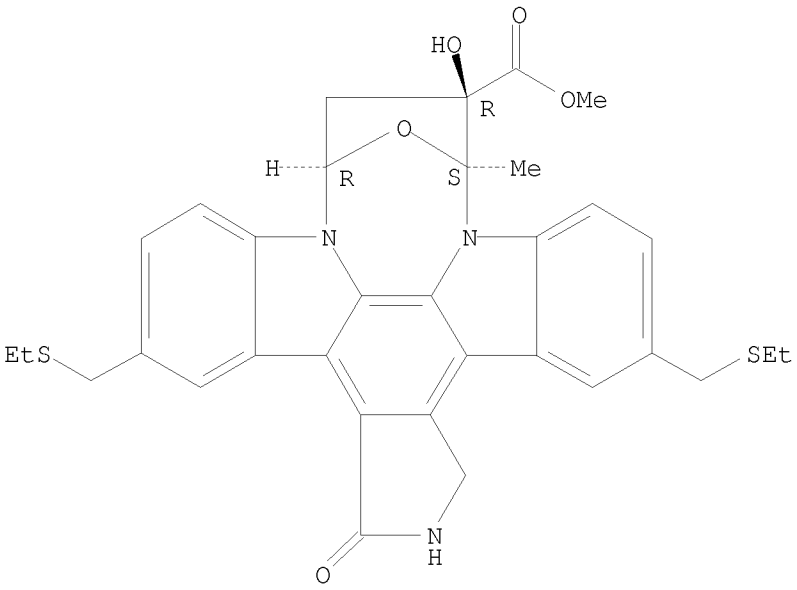
Absolute stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 22 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:627732 CAPLUS
DOCUMENT NUMBER: 141:199768
TITLE: Specific Modulation of Astrocyte Inflammation by Inhibition of Mixed Lineage Kinases with CEP-1347
AUTHOR(S): Falsig, Jeppe; Poerzgen, Peter; Lotharius, Julie; Leist, Marcel
CORPORATE SOURCE: H. Lundbeck, Valby, 2500, Den.
SOURCE: Journal of Immunology (2004), 173(4), 2762-2770
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Inflammatory conversion of murine astrocytes correlates with the activation of various MAPK, and inhibition of terminal MAPKs like JNK or p38 dampens the inflammatory reaction. Mixed lineage kinases (MLKs), a family of MAPK kinase kinases, may therefore be involved in astrocyte inflammation. In this study, we explored the effect of the MLK inhibitors CEP-1347 and CEP-11004 on the activation of murine astrocytes by either TNF plus IL-1 or by a complete cytokine mix containing addnl. IFN-γ. The compds. blocked NO-, PG-, and IL-6 release with a median inhibitory concentration of .apprx.100 nM. This activity correlated with a block of the JNK and the p38 pathways activated in complete cytokine mix-treated astrocytes. Although CEP-1347 did not affect the activation of NF-κB, it blocked the expression of cyclooxygenase-2 and inducible NO synthase at the transcriptional level. Quant. transcript profiling of 17 inflammation-linked genes revealed a specific modulation pattern of astrocyte activation by MLK inhibition, for instance, characterized by up-regulation of the anti-stress factors inhibitor of apoptosis protein-2 and activated transcription factor 4, no effect on manganese superoxide dismutase and caspase-11, and down-regulation of major inflammatory players like TNF, GM-CSF, urokinase-type plasminogen activator, and IL-6. In conclusion, MLK inhibitors like CEP-1347 are highly potent astrocyte immune modulators with a novel spectrum of activity.
IT 156177-65-0, CEP-1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(specific modulation of astrocyte inflammation by inhibition of mixed lineage kinases with CEP-1347)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

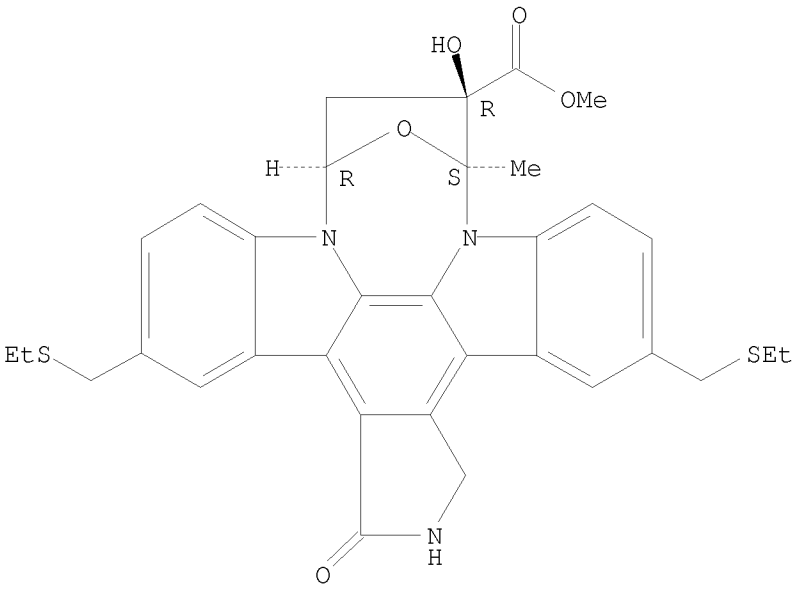
Absolute stereochemistry.



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:558363 CAPLUS
DOCUMENT NUMBER: 142:32487
TITLE: Activation of c-Jun N-terminal kinase mediates gp120IIIB- and nucleoside analogue-induced sensory neuron toxicity
AUTHOR(S): Bodner, Amos; Toth, Peter T.; Miller, Richard J.
CORPORATE SOURCE: Department of Molecular Pharmacology and Biological Chemistry, Feinberg School of Medicine, Northwestern University, Chicago, IL, 60611, USA
SOURCE: Experimental Neurology (2004), 188(2), 246-253
CODEN: EXNEAC; ISSN: 0014-4886
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Peripheral neuropathy is the most common neurol. symptom in patients with acquired immunodeficiency syndrome (AIDS). Here, we examine possible mechanisms of gp120 and nucleoside reverse transcriptase inhibitors (NRTIs) in the pathogenesis of AIDS peripheral neuropathy. Neonatal dorsal root ganglion (DRG) neurons were found to undergo apoptosis in response to chronic treatment with gp120IIIB, an effect enhanced by the co-application of hCD4, as well as upon exposure to the nucleoside reverse transcriptase inhibitor (NRTI), 2',3'-dideoxyinosine (ddI). DRG neurons were rescued from the neurotoxic effects of these agents by CEP-1347, an inhibitor of the mixed lineage kinases (MLKs), upstream activators of the c-Jun N-terminal kinase (JNK) signaling pathway. In addition, gp120- or ddI-mediated toxicity were also inhibited by neuronal expression of dominant neg. versions of the MLKs. Our results suggest that both gp120 and the NRTIs cause sensory neuron apoptosis through the activation of the JNK pathway, and that CEP-1347-like compds. may serve as a therapeutic option in patients with AIDS-associated peripheral neuropathy.
IT 156177-65-0, CEP-1347
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CEP-1347 rescued neonatal rat dorsal root ganglion from neurotoxic effect of gp120 and 2',3'-dideoxyinosine)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:368885 CAPLUS
DOCUMENT NUMBER: 140:386047
TITLE: Cytomodulating peptides and methods for treating neurological disorders
INVENTOR(S): Iyer, Suhasini; Buelow, Roland; Lazarov, Mirella; Fong, Timothy
PATENT ASSIGNEE(S): Sangstat Medical Corporation, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004037196	A2	20040506	WO 2003-US33602	20031024
WO 2004037196	A3	20060330		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003286611	A1	20040513	AU 2003-286611	20031024
US 20040186052	A1	20040923	US 2003-693331	20031024
WO 2005009457	A1	20050203	WO 2004-US15506	20040517
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

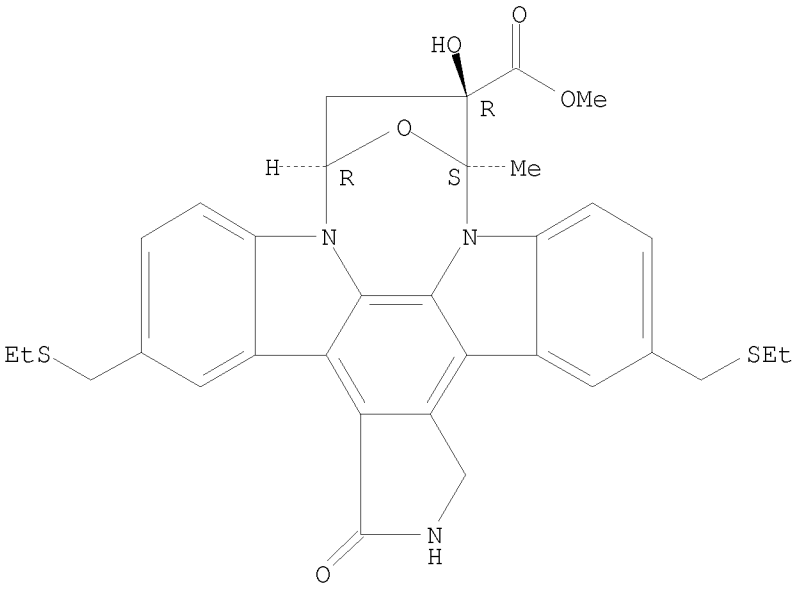
PRIORITY APPLN. INFO.:		
US 2002-421297P	P	20021024
US 2002-431420P	P	20021205
US 2003-470839P	P	20030515
WO 2003-US33602	W	20031024

AB Compns. and methods are provided for inhibiting neuronal cell death and the loss of neuronal contacts resulting from acute and chronic neurol. disorders, including neurodegenerative and neuroinflammatory diseases. The compns. and methods utilize RDP-58 compns. capable of providing a direct neuroprotective effect on neuronal cells in conjunction with inhibition of autoimmune and inflammatory processes.

IT 156177-65-0, CEP-1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cytomodulating peptides and methods for treating neurol. disorders)

RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

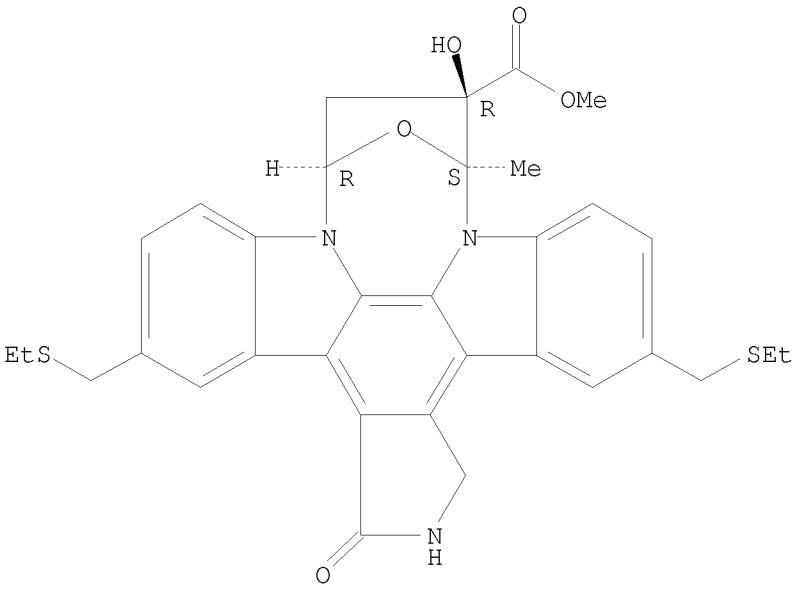
L4 ANSWER 25 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:216615 CAPLUS
DOCUMENT NUMBER: 140:367903
TITLE: Targeting the JNK MAPK cascade for inhibition: basic science and therapeutic potential
AUTHOR(S): Bogoyevitch, Marie A.; Boehm, Ingrid; Oakley, Aaron; Ketterman, Albert J.; Barr, Renae K.
CORPORATE SOURCE: School of Biomedical and Chemical Sciences, Cell Signalling Laboratory, Biochemistry and Molecular Biology, University of Western Australia, Crawley, WA 6009, Australia
SOURCE: Biochimica et Biophysica Acta, Proteins and Proteomics (2004), 1697(1-2), 89-101
CODEN: BBAPBW; ISSN: 1570-9639
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The c-Jun N-terminal protein kinases (JNKs) form one subfamily of the mitogen-activated protein kinase (MAPK) group of serine/threonine protein kinases. The JNKs were first identified by their activation in response to a variety of extracellular stresses and their ability to phosphorylate the N-terminal transactivation domain of the transcription factor c-Jun. One approach to study the function of the JNKs has included in vivo gene knockouts of each of the three JNK genes. While loss of either JNK1 or JNK2 alone appears to have no serious consequences, their combined knockout is embryonic lethal. In contrast, the loss of JNK3 is not embryonic lethal, but rather protects the adult brain from glutamate-induced excitotoxicity. This latter example has generated considerable enthusiasm with JNK3, considered an appropriate target for the treatment of diseases in which neuronal death should be prevented (e.g. stroke, Alzheimer's and Parkinson's diseases). More recently, these gene knockout animals have been used to demonstrate that JNK could provide a suitable target for the protection against obesity and diabetes and that JNKs may act as tumor suppressors. Considerable effort is being directed to the development of chemical inhibitors of the activators of JNKs (e.g. CEP-1347, an inhibitor of the MLK family of JNK pathway activators) or of the JNKs themselves (e.g. SP600125, a direct inhibitor of JNK activity). These most commonly used inhibitors have demonstrated efficacy for use in vivo, with the successful intervention to decrease brain damage in animal models (CEP-1347) or to ameliorate some of the symptoms of arthritis in other animal models (SP600125). Alternative peptide-based inhibitors of JNKs are now also in development. The possible identification of allosteric modifiers rather than direct ATP competitors could lead to inhibitors of unprecedented specificity and efficacy.

IT 156177-65-0, CEP-1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(JNK MAPK cascade inhibitors and their therapeutic potential)

RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



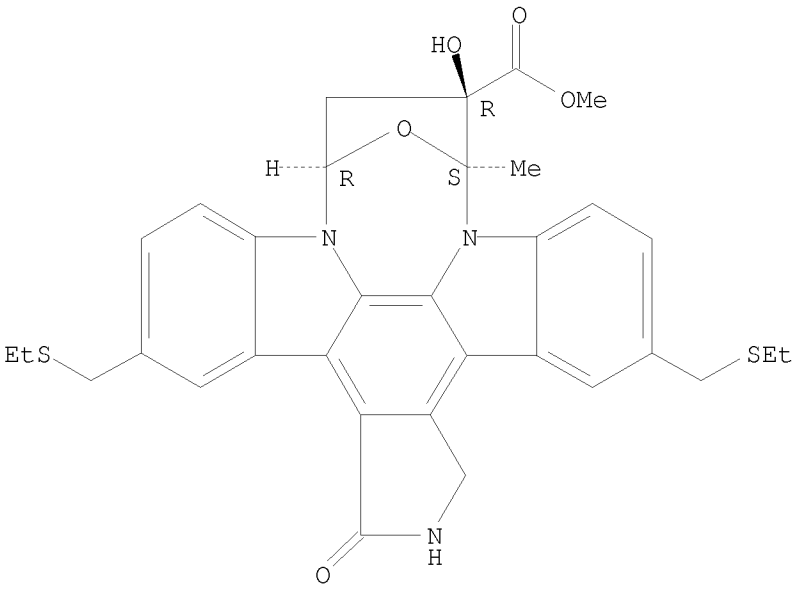
REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 26 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:192143 CAPLUS
DOCUMENT NUMBER: 140:419104
TITLE: Inhibition of mixed lineage kinase 3 attenuates MPP+-induced neurotoxicity in SH-SY5Y cells
AUTHOR(S): Mathiasen, Joanne R.; McKenna, Beth Ann W.; Saporito, Michael S.; Ghadge, Ghanashyam D.; Roos, Raymond P.; Holskin, Beverly P.; Wu, Zhi-Liang; Trusko, Stephen P.; Connors, Thomas C.; Maroney, Anna C.; Thomas, Beth Ann; Thomas, Jeffrey C.; Bozyczko-Coyne, Donna
CORPORATE SOURCE: Neurobiology, Cephalon, Inc., West Chester, PA, 19380, USA
SOURCE: Brain Research (2004), 1003(1,2), 86-97
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The neuropathol. of Parkinson's Disease has been modeled in exptl. animals following MPTP treatment and in dopaminergic cells in culture treated with the MPTP neurotoxic metabolite, MPP+. MPTP through MPP+ activates the stress-activated c-Jun N-terminal kinase (JNK) pathway in mice and SH-SY5Y neuroblastoma cells. Recently, it was demonstrated that CEP-1347/KT7515 attenuated MPTP-induced nigrostriatal dopaminergic neuron degeneration in mice, as well as MPTP-induced JNK phosphorylation. Presumably, CEP-1347 acts through inhibition of at least one upstream kinase within the mixed lineage kinase (MLK) family since it has been shown to inhibit MLK 1, 2 and 3 in vitro. Activation of the MLK family leads to JNK activation. In this study, the potential role of MLK and the JNK pathway was examined in MPP+-induced cell death of differentiated SH-SY5Y cells using CEP-1347 as a pharmacol. probe and dominant neg. adenoviral constructs to MLKs. CEP-1347 inhibited MPP+-induced cell death and the morphol. features of apoptosis. CEP-1347 also prevented MPP+-induced JNK activation in SH-SY5Y cells. Endogenous MLK 3 expression was demonstrated in SH-SY5Y cells through protein levels and RT-PCR. Adenoviral infection of SH-SY5Y cells with a dominant neg. MLK 3 construct attenuated the MPP+-mediated increase in activated JNK levels and inhibited neuronal death following MPP+ addition compared to cultures infected with a control construct. Adenoviral dominant neg. constructs of two other MLK family members (MLK 2 and DLK) did not protect against MPP+-induced cell death. These studies show that inhibition of the MLK 3/JNK pathway attenuates MPP+-mediated SH-SY5Y cell death in culture and supports the mechanism of action of CEP-1347 as an MLK family inhibitor.

IT 156177-65-0, CEP-1347
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of mixed lineage kinase 3 attenuates MPP+-induced neurotoxicity in SH-SY5Y cells)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

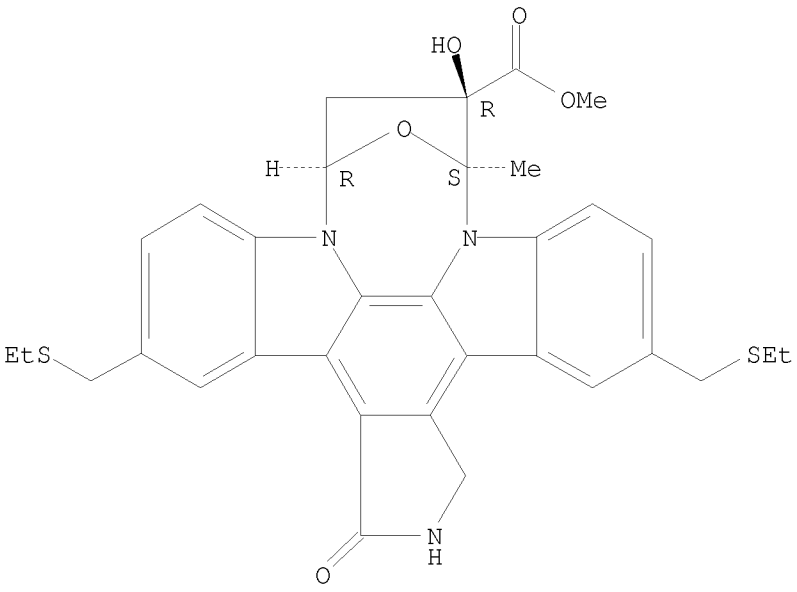
Absolute stereochemistry.



REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

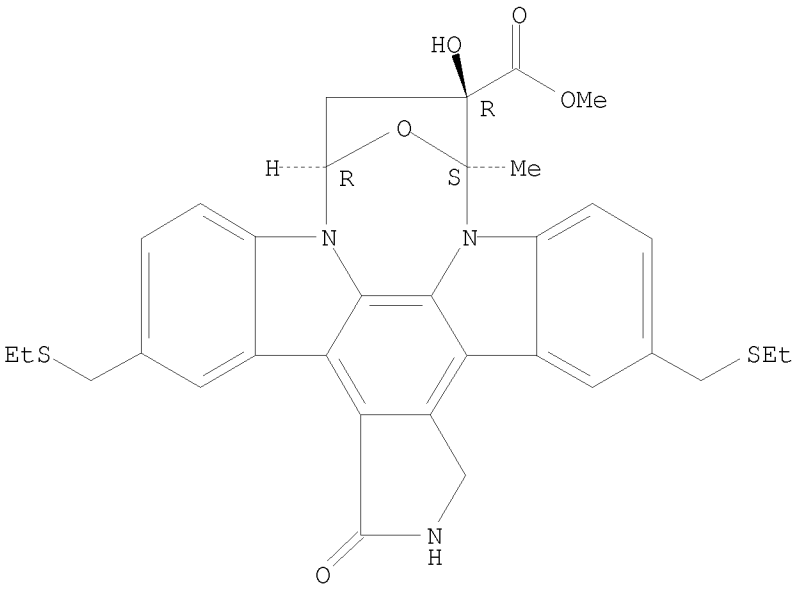
L4 ANSWER 27 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:166596 CAPLUS
DOCUMENT NUMBER: 141:219278
TITLE: Signaling pathways implicated in p75 neurotrophin receptor-mediated neuronal survival and death
AUTHOR(S): Roux, Philippe P.
CORPORATE SOURCE: McGill Univ., Montreal, QC, Can.
SOURCE: (2002) 215 pp. Avail.: UMI, Order No. DANQ78761
From: Diss. Abstr. Int., B 2003, 64(4), 1640
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable
IT 156177-65-0, CEP 1347
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); BIOL (Biological study)
(signaling pathways implicated in p75 neurotrophin receptor-mediated neuronal survival and death)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 28 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:102156 CAPLUS
DOCUMENT NUMBER: 140:229249
TITLE: Improvement of embryonic dopaminergic neurone survival in culture and after grafting into the striatum of hemiparkinsonian rats by CEP-1347
AUTHOR(S): Boll, Jette Bisgaard; Geist, Marie Aavang; Schierle, Gabriele S. Kaminski; Petersen, Karina; Leist, Marcel; Vaudano, Elisabetta
CORPORATE SOURCE: Department of Molecular Disease Biology, H. Lundbeck A/S, Valby, Den.
SOURCE: Journal of Neurochemistry (2004), 88(3), 698-707
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Transplantation of embryonic nigral tissue ameliorates functional deficiencies in Parkinson's disease (PD). A main constraint of neural grafting is the poor survival of dopaminergic neurons grafted into patients. Studies in rats indicated that many grafted neurons die by apoptosis. CEP-1347 is a mixed-lineage-kinase (MLK) inhibitor with neuroprotective action in several in vitro and in vivo models of neuronal apoptosis. We studied the effect of CEP-1347 on the survival of embryonic rat dopaminergic neurons in culture, and after transplantation in hemiparkinsonian rats. CEP-1347 and the alternative MLK inhibitor CEP-11004 significantly increased the survival of dopaminergic neurons in primary cultures from rat ventral mesencephalon and in Mn2+-exposed PC12 cells, a surrogate model of dopaminergic lethal stress. Moreover, combined treatment of the grafting cell suspension and the host animal with CEP-1347 significantly improved the long-term survival of rat dopaminergic neurons transplanted into the striatum of hemiparkinsonian rats. Also, the protective effect of CEP-1347 resulted in an increase in total graft size and in enhanced fiber outgrowth. Thus, treatment with CEP-1347 improved dopaminergic cell survival under severe stress and might be useful to improve the pos. outcome of transplantation therapy in PD and reduce the amount of human tissue required.
IT 156177-65-0, CEP-1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(improvement of embryonic dopaminergic neuron survival in culture and after grafting into the striatum of hemiparkinsonian rats by CEP-1347)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

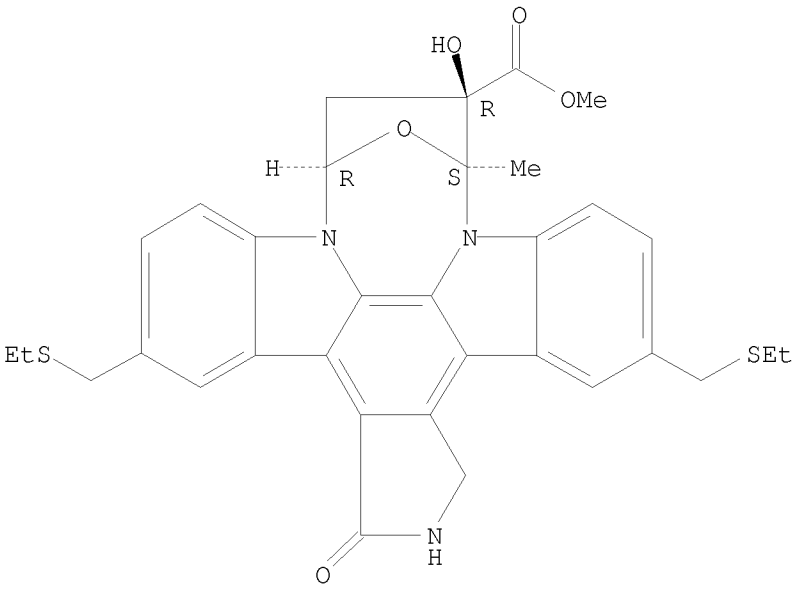
Absolute stereochemistry.



REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 29 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:11004 CAPLUS
DOCUMENT NUMBER: 141:82110
TITLE: The safety and tolerability of a mixed lineage kinase inhibitor (CEP-1347) in PD
AUTHOR(S): Schwid, Steven; Shoulson, Ira; Marek, Ken; Oakes, David; Kieburtz, Karl; Gorbold, Emily; Fahn, Stanley; Goetz, Christopher; Rudolph, Alice; Shinaman, Aileen
CORPORATE SOURCE: Parkinson Study Group, Department of Neurology, University of Rochester Medical Center, Rochester, NY, 14642, USA
SOURCE: Neurology (2004), 62(2), 330-332
CODEN: NEURAI; ISSN: 0028-3878
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CEP-1347 is an inhibitor of members of the mixed lineage kinase family, key signals triggering apoptotic neuronal death. The authors performed a randomized, blinded, placebo-controlled study assessing the safety, tolerability, pharmacokinetics, and acute symptomatic effects of CEP-1347 in 30 patients with Parkinson's disease (PD). In this short-term study, CEP-1347 was safe and well tolerated. It had no acute effect on parkinsonian symptoms or levodopa pharmacokinetics, making it well suited for larger and longer studies of its potential to modify the course of PD.
IT 156177-65-0, CEP-1347
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CEP-1347 safety, tolerability, and effect on levodopa pharmacokinetics in Parkinson's disease)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

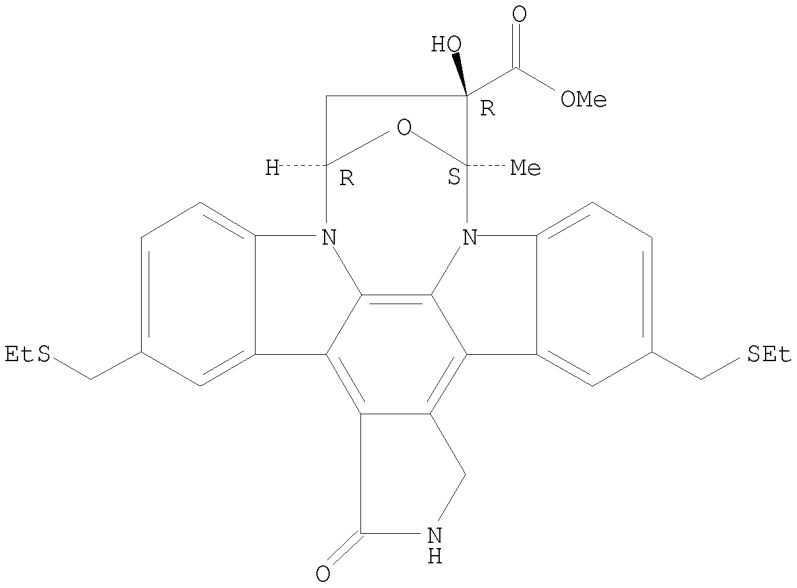
L4 ANSWER 30 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:855794 CAPLUS
DOCUMENT NUMBER: 139:345938
TITLE: Combination therapy including cyclooxygenase 2 (COX2) inhibitor(s) for the treatment of Parkinson's disease
INVENTOR(S): Stephenson, Diane T.; Isakson, Peter C.; Maziasz, Timothy J.
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 266 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003088958	A2	20031030	WO 2003-US11269	20030414
WO 2003088958	A3	20040819		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2481934	A1	20031030	CA 2003-2481934	20030414
AU 2003223579	A1	20031103	AU 2003-223579	20030414
US 20040034083	A1	20040219	US 2003-413348	20030414
EP 1494664	A2	20050112	EP 2003-719717	20030414
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003009259	A	20050209	BR 2003-9259	20030414
JP 2005528403	T	20050922	JP 2003-585710	20030414
MX 2004009352	A	20050125	MX 2004-9352	20040924
PRIORITY APPLN. INFO.:			US 2002-373311P P	20020418
			WO 2003-US11269 W	20030414

OTHER SOURCE(S): MARPAT 139:345938
AB The invention discloses a method for treating, preventing, or inhibiting Parkinson's disease (PD) in a subject in need of such treatment, inhibition, or prevention. The method comprises treating the subject with one or more COX2 selective inhibitor(s) or isomer(s) or pharmaceutically acceptable salt(s), ester(s), or prodrug(s) thereof, in combination with one or more second drugs, wherein the amount of the COX2 selective inhibitor(s) or isomer(s) or pharmaceutically acceptable salt(s), ester(s), or prodrug(s) thereof in combination with the amount of second drug(s) constitutes a PD treatment-, inhibition- or prevention-effective amount
IT 156177-65-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy including cyclooxygenase 2 inhibitor for treatment of Parkinson's disease)
RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

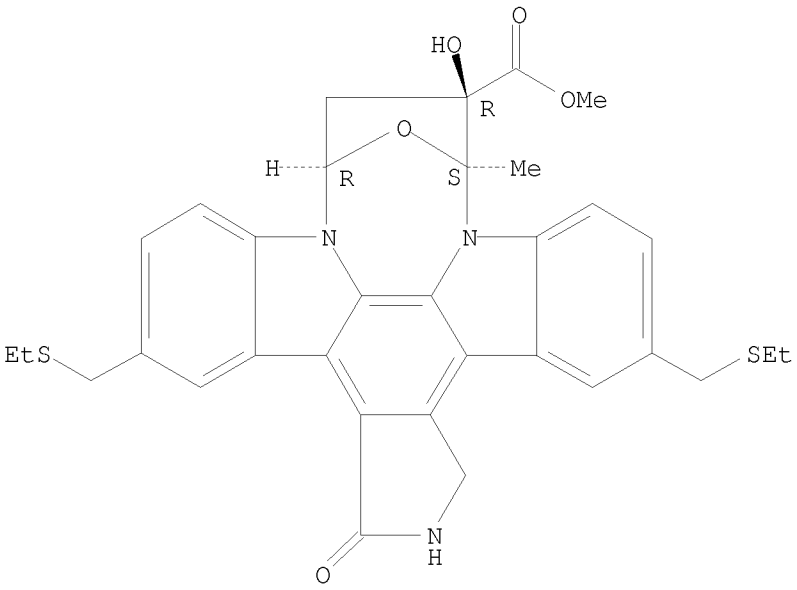
Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 31 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:469001 CAPLUS
DOCUMENT NUMBER: 139:358581
TITLE: CEP-1347 promotes survival of NGF responsive neurones in primary DRG explants
AUTHOR(S): Bilsland, James G.; Harper, Sarah J.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Merck, Sharp, and Dohme Research Laboratories, Harlow, CM20 2QR, UK
SOURCE: NeuroReport (2003), 14(7), 995-999
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CEP-1347 inhibits the signaling pathway of c-jun-N-terminal kinase, and is neuroprotective in vivo and in vitro. Embryonic chick dorsal root ganglion neurons are dependent on NGF for survival and neurite outgrowth; NGF withdrawal results in apoptotic cell death. We examined the neuroprotective and neurite outgrowth promoting activity of CEP-1347 in dissociated DRG neurons and in primary DRG explants. CEP-1347 was as effective as NGF in promoting survival of dissociated DRG neurons, but caused only limited neurite outgrowth from DRG explants. When NGF was subsequently added to CEP-1347 treated explants, the outgrowth increased to a similar level to explants which had received NGF throughout. CEP-1347 may be a useful tool to maintain viable DRG explants to allow evaluation of neurite outgrowth promoting compds. and dissection of survival and neurite outgrowth signaling pathways.
IT 156177-65-0, CEP-1347
RL: PAC (Pharmacological activity); BIOL (Biological study)
(CEP-1347 neuroprotective and neurite outgrowth promoting activity in dissociated embryonic chick dorsal root ganglion neurons and in primary dorsal root explants and NGF effect thereon)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



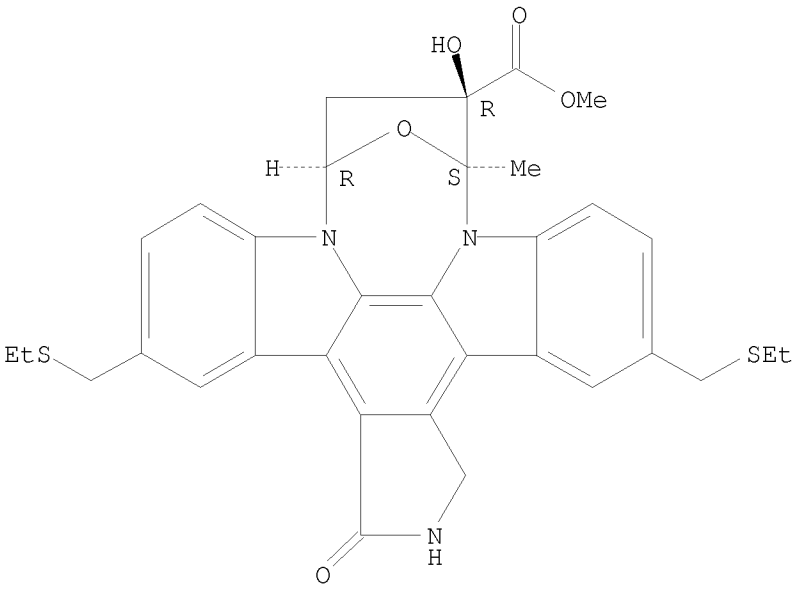
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 32 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:459116 CAPLUS
DOCUMENT NUMBER: 139:147985
TITLE: JNK-independent Activation of c-Jun during Neuronal Apoptosis Induced by Multiple DNA-damaging Agents
AUTHOR(S): Besirli, Cagri Giray; Johnson, Eugene Malcolm, Jr.
CORPORATE SOURCE: Departments of Neurology and Molecular Biology and Pharmacology, Washington University School of Medicine, St. Louis, MO, 63110, USA
SOURCE: Journal of Biological Chemistry (2003), 278(25), 22357-22366
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Activation of the JNK pathway and induction of the AP-1 transcription factor c-Jun are critical for neuronal apoptosis caused by a variety of insults. Ara-C-induced DNA damage caused rapid sympathetic neuronal death that was associated with an increase of c-jun expression. In addition, c-Jun was phosphorylated in its N-terminal transactivation domain, which is important for c-Jun-mediated gene transcription. Blocking c-Jun activation by JNK pathway inhibition prevented neuronal death after stress. In contrast, neither the JNK inhibitor SP600125 nor the mixed lineage kinase inhibitor CEP-1347 prevented cytosine arabinoside-induced neuronal death, demonstrating that the JNK pathway was not necessary for DNA damage-induced neuronal apoptosis. Surprisingly, SP600125 or CEP-1347 could not block c-Jun induction or phosphorylation after DNA damage. Pharmacol. inhibitors of cyclin-dependent kinase (CDK) activity completely prevented c-Jun phosphorylation after DNA damage. These results demonstrate that c-Jun activation during DNA damage-induced neuronal apoptosis was independent of the classical JNK pathway and was mediated by a novel c-Jun kinase. Based on pharmacol. criteria, DNA damage-induced neuronal c-Jun kinase may be a member of the CDK family or be activated by a CDK-like kinase. Activation of this novel kinase and subsequent phosphorylation of c-Jun may be important in neuronal death after DNA damage.

IT 156177-65-0, CEP-1347
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mixed lineage kinase inhibitor; neither the SP600125 nor the CEP-1347 prevented cytosine arabinoside-induced neuronal death, demonstrating that the JNK pathway was not necessary for DNA damage-induced neuronal apoptosis)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

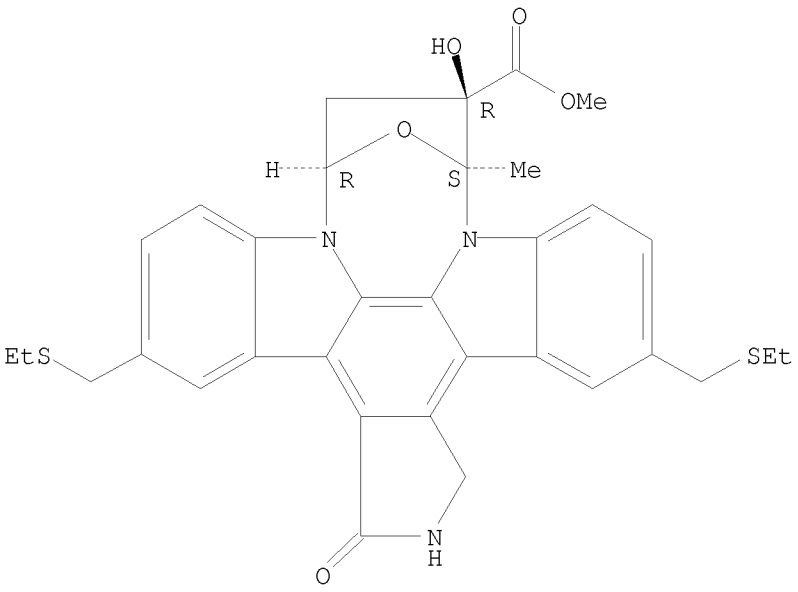
Absolute stereochemistry.



REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 33 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:400387 CAPLUS
DOCUMENT NUMBER: 139:110946
TITLE: CEP-1347, Cephalon
AUTHOR(S): Mucke, Hermann A. M.
CORPORATE SOURCE: HM Pharma Consultancy, Vienna, A-1160, Austria
SOURCE: IDrugs (2003), 6(4), 377-383
CODEN: IDRUFN; ISSN: 1369-7056
PUBLISHER: Current Drugs
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. CEP-1347 is an indolocarbazole choline acetyltransferase inhibitor and a c-Jun N-terminal kinase inhibitor, under development by Cephalon Inc, H. Lundbeck A/S and Kyowa Hakko Kogyo Co. Ltd. for the potential treatment of Alzheimer's disease, Parkinson's disease and HIV-related peripheral neuropathy.
IT 156177-65-0P, CEP 1347
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(CEP 1347 pharmacol. for treatment of Parkinson's disease, Alzheimer's disease, and HIV-related peripheral neuropathy)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 34 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:153388 CAPLUS
DOCUMENT NUMBER: 138:198569
TITLE: Use of kinase-inhibiting agents for prophylaxis and/or therapy of viral diseases, and system for identification of such agents
INVENTOR(S): Ludwig, Stephan; Planz, Oliver; Sedlacek, Hans-Harald; Pleschka, Stephan
PATENT ASSIGNEE(S): Medinnova Gesellschaft fur Medizinische Innovationen aus Akademischer Forschung m.b.H., Germany
SOURCE: Ger. Offen., 10 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

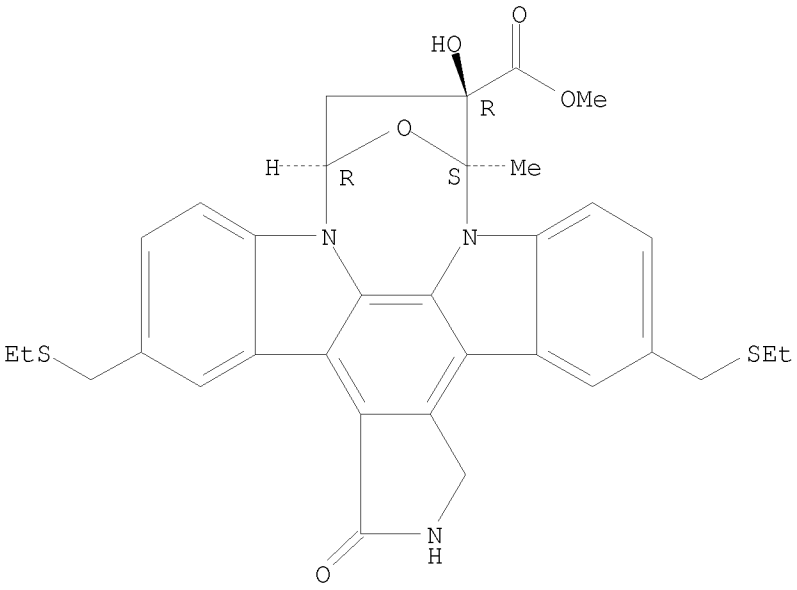
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10138912	A1	20030227	DE 2001-10138912	20010808
WO 2003015689	A2	20030227	WO 2002-DE2810	20020726
WO 2003015689	A3	20040617		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002325169	A1	20030303	AU 2002-325169	20020726
EP 1450778	A2	20040901	EP 2002-758125	20020726
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2005506975	T	20050310	JP 2003-520450	20020726
EP 1707193	A2	20061004	EP 2006-90076	20020726
EP 1707193	A3	20071121		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR, BG, CZ, EE, SK				
US 20050129694	A1	20050616	US 2005-486313	20050210

PRIORITY APPLN. INFO.:			
DE 2001-10138912	A	20010808	
EP 2002-758125	A3	20020726	
WO 2002-DE2810	W	20020726	

AB The invention discloses the use of at least one, preferably two, active substance(s) for the prophylaxis and/or therapy of at least one viral disease, characterized in that the active substance(s) inhibit either a signal transduction pathway-associated kinase such that virus replication is essentially inhibited or a SEK kinase.
IT 156177-65-0, CEP 1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kinase-inhibiting agents for prophylaxis and/or therapy of viral diseases, and system for identification of such agents)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-

i][1,6]benzodiazocine-10-carboxylic acid,
5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

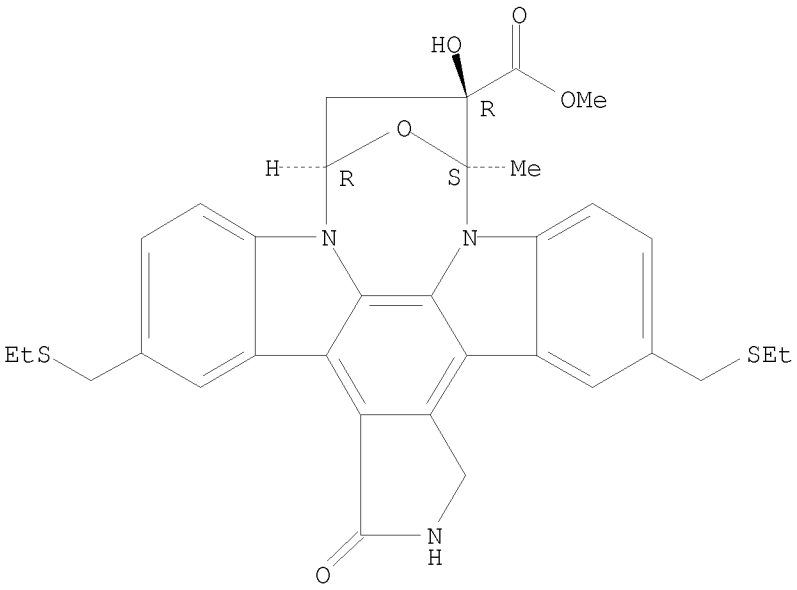
Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 35 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:972955 CAPLUS
DOCUMENT NUMBER: 139:127133
TITLE: Discovery of CEP-1347/KT-7515, an inhibitor of the JNK/SAPK pathway for the treatment of neurodegenerative diseases
AUTHOR(S): Saporito, Michael S.; Hudkins, Robert L.; Maroney, Anna C.
CORPORATE SOURCE: Departments of Medicinal Chemistry, Neurobiology, Cephalon Inc., West Chester, PA, 19380, USA
SOURCE: Progress in Medicinal Chemistry (2002), 40, 23-62
CODEN: PMDCAY; ISSN: 0079-6468
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Apoptosis has been proposed as a mechanism of cell death in Alzheimer's, Huntington's and Parkinson's diseases and the occurrence of apoptosis in these disorders suggests a common mechanism. Events such as oxidative stress, calcium toxicity, mitochondria defects, excitatory toxicity, and deficiency of survival factors are all postulated to play varying roles in the pathogenesis of the diseases. However, the transcription factor c-jun may play a role in the pathol. and cell death processes that occur in Alzheimer's disease. Parkinson's disease (PD) is also a progressive disorder involving the specific degeneration and death of dopamine neurons in the nigrostriatal pathway. In Parkinson's disease, dopaminergic neurons in the substantia nigra are hypothesized to undergo cell death by apoptotic processes. The commonality of biochem. events and pathways leading to cell death in these diseases continues to be an area under intense investigation. The current therapy for PD and AD remains targeting replacement of lost transmitter, but the ultimate objective in neurodegenerative therapy is the functional restoration and/or cessation of progression of neuronal loss. This chapter will describe a novel approach for the treatment of neurodegenerative diseases through the development of kinase inhibitors that block the active cell death process at an early transcriptional independent step in the stress activated kinase cascade. In particular, preclin. data will be presented on the c-Jun Amino Kinase pathway inhibitor, CEP-1347/KT-7515, with respect to its properties that make it a desirable clin. candidate for treatment of various neurodegenerative diseases.
IT 156177-65-0, CEP-1347
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(discovery of CEP-1347/KT-7515, an inhibitor of JNK/SAPK pathway for treatment of neurodegenerative diseases)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

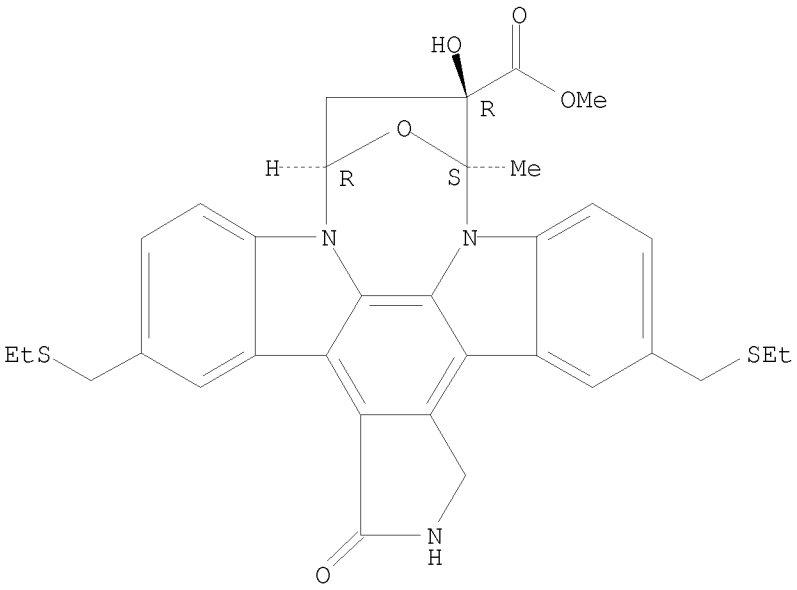
Absolute stereochemistry.



REFERENCE COUNT: 174 THERE ARE 174 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 36 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:952718 CAPLUS
DOCUMENT NUMBER: 138:396045
TITLE: K252a and CEP1347 are Neuroprotective Compounds that Inhibit Mixed-Lineage Kinase-3 and Induce Activation of Akt and ERK
AUTHOR(S): Roux, Philippe P.; Dorval, Genevieve; Boudreau, Mathieu; Angers-Loustau, Alexandre; Morris, Stephen J.; Makkerh, Joe; Barker, Philip A.
CORPORATE SOURCE: Montreal Neurological Institute, Centre for Neuronal Survival, McGill University, Montreal, QC, H3A 2B4, Can.
SOURCE: Journal of Biological Chemistry (2002), 277(51), 49473-49480
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB K252a is best known as a Trk inhibitor, but is also a neuroprotective compound CEP1347, a K252a derivative, retains neuroprotective properties, but does not inhibit TrkA. CEP1347 has recently been shown to directly inhibit MAPKKKs, including MLK3, but the effect of K252a on MAPKKKs remains unknown. K252a and CEP1347 not only prevent death, but also facilitate neurite outgrowth and maintenance, somal hypertrophy, and neurotransmitter synthesis. The biochem. basis for these trophic effects remains unknown. We have compared the effects of CEP1347 and K252a on MLK and JNK signaling and on neurotrophic pathways that support survival and growth. Our data show that K252a is a potent inhibitor of MLK3 activity in vivo and in vitro (IC50 .apprx. 5 nM). However, we also found that K252a and CEP1347 activate Akt and ERK and show that blockade of phosphatidylinositol 3-kinase or MEK activity ablates the effect of K252a and CEP1347 on cell survival. Activation of Akt and ERK occurs through an MLK-independent pathway that may involve c-Src. Together, these data show that the neuroprotective and neurotrophic effects of K252a and CEP1347 involve activation of several neurotrophic signaling pathways.
IT 156177-65-0, CEP1347
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(K252a and CEP1347 are neuroprotective compds. that inhibit mixed-lineage kinase-3 and induce activation of Akt and ERK)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

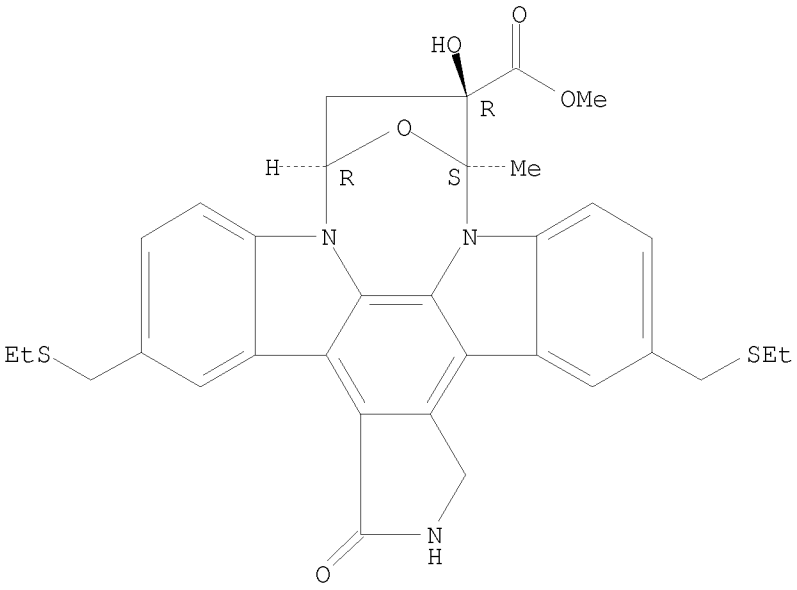
L4 ANSWER 37 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:888538 CAPLUS
DOCUMENT NUMBER: 137:363091
TITLE: Pyrrolocarbazoles for the treatment and prevention of pain
INVENTOR(S): Aimone, Lisa D.; Hudkins, Robert L.; Miller, Mathew S.
PATENT ASSIGNEE(S): Cephalon, Inc., USA
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002092065	A2	20021121	WO 2002-US15667	20020516
WO 2002092065	A3	20030731		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 20030087899	A1	20030508	US 2002-146680	20020515
US 7018999	B2	20060328		
CA 2447091	A1	20021121	CA 2002-2447091	20020516
AU 2002342715	A1	20021125	AU 2002-342715	20020516
EP 1389100	A2	20040218	EP 2002-769765	20020516
EP 1389100	B1	20081008		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
MX 2003010451	A	20040505	MX 2003-10451	20020516
JP 2004534751	T	20041118	JP 2002-588983	20020516
AT 410201	T	20081015	AT 2002-769765	20020516
ES 2314101	T3	20090316	ES 2002-769765	20020516
PRIORITY APPLN. INFO.:			US 2001-291227P P	20010516
			US 2002-146680 A	20020515
			WO 2002-US15667 W	20020516

OTHER SOURCE(S): MARPAT 137:363091
AB Novel methods for the treatment and/or prevention of pain are presented. The methods may comprise administering to a subject in need thereof an effective amount of a stress-activated protein kinase inhibitor. Preferred compds. for use in the methods include fused pyrrolocarbazole compds. Thus, a pyrrolocarbazole derivative was administered at s.c. at doses of 1.0 mg/kg in 30% Solutol 24 h prior to the formalin challenge. The compound demonstrated activity for the prevention and/or treatment of pain according to the formalin model and a decrease in the flinching/shaking responses of about 15% in phase I and about 30% in phase II. was observed
IT 156177-65-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pyrrolocarbazoles for treatment and prevention of pain)

RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

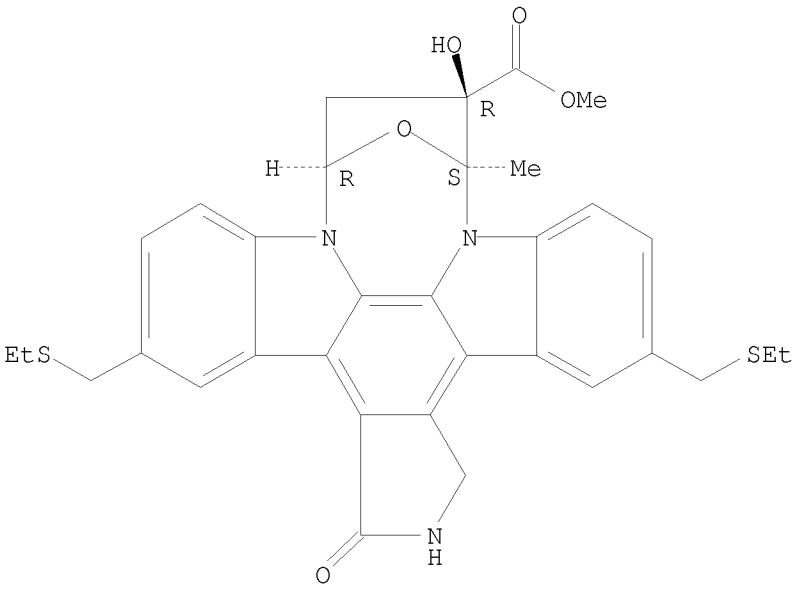
Absolute stereochemistry.



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 38 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:749210 CAPLUS
DOCUMENT NUMBER: 137:309328
TITLE: Mixed lineage kinase 3 mediates gp120IIIB-induced neurotoxicity
AUTHOR(S): Bodner, Amos; Maroney, Anna C.; Finn, James P.; Ghadge, Ghanashyam; Roos, Raymond; Miller, Richard J.
CORPORATE SOURCE: Department of Molecular Pharmacology and Biological Chemistry, Northwestern University, Chicago, IL, 60611, USA
SOURCE: Journal of Neurochemistry (2002), 82(6), 1424-1434
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Overexpression of gp120, the major coat protein of the HIV-1 virus, in central glial cells, or treatment of neurons with gp120 in culture, produces apoptotic neuronal death. Here the authors demonstrate that CEP-1347 (KT7515), an inhibitor of mixed lineage kinase 3 (MLK3), an upstream activator of JNK, inhibits gp120IIIB-induced apoptosis of hippocampal neurons. Furthermore, expression of wild type MLK3 in hippocampal pyramidal neurons enhanced gp120IIIB-induced neurotoxicity, whereas expression of a dominant neg. MLK3 protected neurons from the toxic effects of the glycoprotein. These results indicate a role for MLK3 signaling in gp120IIIB-induced neuronal death, and suggest potential clin. utility of CEP-1347 in inhibiting the progression of AIDS dementia.
IT 156177-65-0, CEP-1347
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mixed lineage kinase 3 mediates gp120IIIB-induced neurotoxicity)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

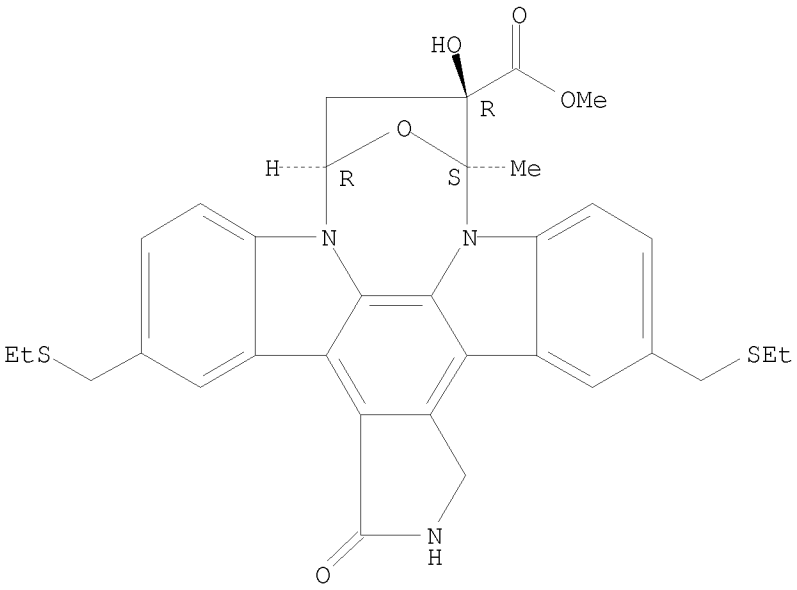
Absolute stereochemistry.



REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 39 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:438459 CAPLUS
DOCUMENT NUMBER: 138:117597
TITLE: Blockade of c-Jun N-terminal kinase pathway attenuates gentamicin-induced cochlear and vestibular hair cell death
AUTHOR(S): Ylikoski, Jukka; Liang, Xing-Qun; Virkkala, Jussi; Pirvola, Ulla
CORPORATE SOURCE: Institute of Biotechnology, University of Helsinki, Helsinki, 00014, Finland
SOURCE: Hearing Research (2002), 166(1-2), 33-43
CODEN: HERED3; ISSN: 0378-5955
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The ototoxic action of aminoglycoside antibiotics leading to the loss of inner ear hair cells is well documented. However, the mol. mechanisms are poorly defined. We have previously shown that in neomycin-exposed cochlear organotypic cultures, the c-Jun N-terminal kinase (JNK) pathway - associated with stress, injury and apoptosis - is activated in hair cells. We have shown that hair cell death can be attenuated by CEP-1347, an inhibitor of JNK signaling. In the present study, we demonstrate that gentamicin-induced ototoxicity leads to JNK activation and apoptosis in the inner ear hair cells in vivo. We show that systemic administration of CEP-1347 attenuates gentamicin-induced decrease of auditory sensitivity and cochlear hair cell damage. In addition, CEP-1347 treatment reduces the extent of hair cell loss in the ampullary cristae after gentamicin intoxication. Particularly, the inner hair cells of the cochlea and type I hair cells of the vestibular organs are protected. Our previous data have shown that also acoustic overstimulation can cause apoptotic death of cochlear hair cells and that CEP-1347 can attenuate noise-induced hair cell loss. Thus, our results imply that activation of JNK cascade may be a common mol. outcome of cellular stress in the inner ear sensory epithelia and that attenuation of the lesion can be provided by inhibiting JNK activation.
IT 156177-65-0, CEP-1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blockade of JNK pathway attenuates gentamicin-induced cochlear and vestibular hair cell death)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

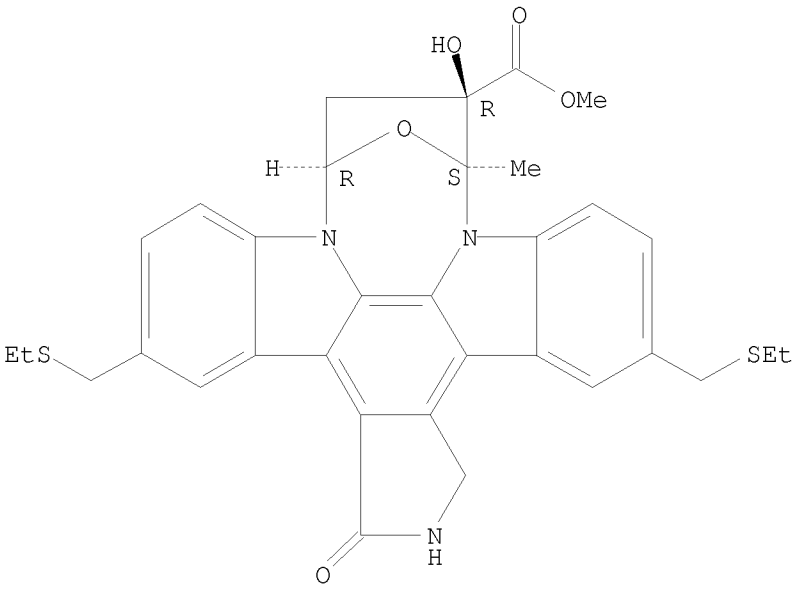
Absolute stereochemistry.



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 40 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:394536 CAPLUS
DOCUMENT NUMBER: 137:304091
TITLE: Mixed lineage kinase family, potential targets for preventing neurodegeneration
AUTHOR(S): Maroney, Anna C.; Saporito, Michael S.; Hudkins, Robert L.
CORPORATE SOURCE: Cephalon Inc., West Chester, PA, 19380, USA
SOURCE: Current Medicinal Chemistry: Central Nervous System Agents (2002), 2(2), 143-155
CODEN: CMCCCO; ISSN: 1568-0150
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The c-Jun amino terminal kinase (JNK) cascade leading to c-Jun phosphorylation has been implicated in the neuronal cellular response to a variety of external stimuli including free radical oxidative stress, trophic withdrawal, amyloid toxicity and activation by death domain receptor ligands. Although the exact causes of neuronal loss in neurodegenerative diseases remain unknown, it has been hypothesized that response to these environmental stresses may be contributing factors. Agents which block the JNK signaling cascade have been proposed as a therapeutic approach for preventing neuronal cell death observed in a variety of neurodegenerative diseases including Parkinson's, Huntington's, and Alzheimer's disease. The JNKs are regulated through a sequential signaling cascade by a series of upstream kinases including the mixed lineage kinases (MLKs). Herein, we review the MLK family as a therapeutic target and provide evidence with CEP-1347, the most advanced MLK inhibitor currently in clin. trials for Parkinson's disease, that intervention at the MLK point in the JNK cascade may reduce the susceptibility of neurons to degenerate.
IT 156177-65-0, CEP-1347
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mixed lineage kinase family, potential targets for preventing neurodegeneration)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

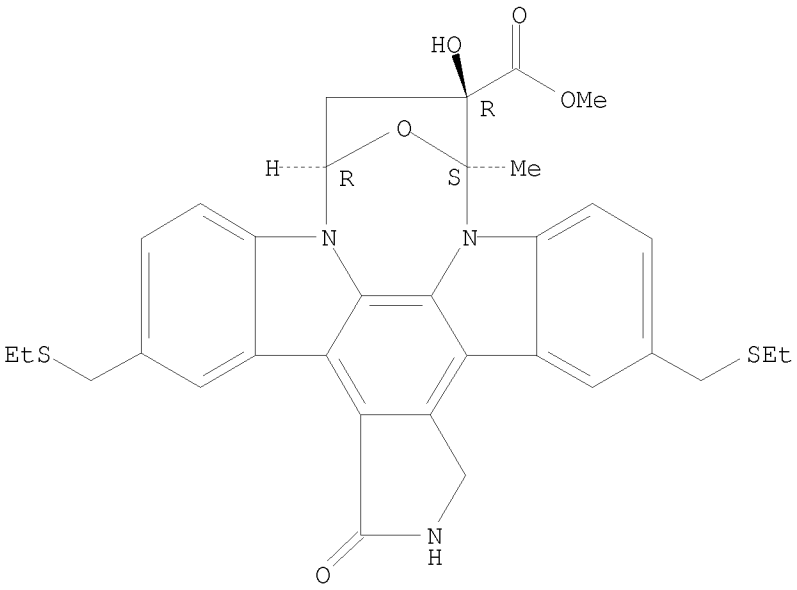
Absolute stereochemistry.



REFERENCE COUNT: 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 41 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:199486 CAPLUS
DOCUMENT NUMBER: 137:41220
TITLE: Generic method for on-line extraction of drug substances in the presence of biological matrices using turbulent flow chromatography
AUTHOR(S): Herman, J. L.
CORPORATE SOURCE: Cephalon, Inc., West Chester, PA, 19380-4245, USA
SOURCE: Rapid Communications in Mass Spectrometry (2002), 16(5), 421-426
CODEN: RCMSEF; ISSN: 0951-4198
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The use of liquid chromatog./mass spectrometry (LC/MS) to quantify drugs in biol. matrixes has been well established over the last decade. Extremely fast LC/MS methods are commonplace in the pharmaceutical industry for high-throughput Absorption, Distribution, Metabolism and Excretion (ADME) screening. However, to truly take full advantage of high-throughput ADME screening, a generic method is needed that eliminates the need to develop a new method for each new compound being screened. New developments in the stationary phase of turbulent flow columns has allowed us to develop an online biol. sample cleanup method that is suitable for over 99% of the compds. in the Cephalon database.
IT 156177-65-0, CEP-1347
RL: ANT (Analyte); ANST (Analytical study)
(generic method for online extraction of drug substances in presence of biol. matrixes using turbulent flow chromatog.)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 42 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:142907 CAPLUS
DOCUMENT NUMBER: 136:194260
TITLE: Methods for modulating multiple lineage kinase proteins and screening compounds which modulate multiple linease kinase proteins
INVENTOR(S): Maroney, Anna; Walton, Kevin M.; Dionne, Craig A.; Neff, Nicola; Knight, Ernest, Jr.; Glicksman, Marcie A.
PATENT ASSIGNEE(S): Cephalon, Inc., USA
SOURCE: PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002014536	A2	20020221	WO 2001-US24822	20010808
WO 2002014536	A3	20030130		
WO 2002014536	A9	20031218		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2419985	A1	20020221	CA 2001-2419985	20010808
AU 2001083179	A	20020225	AU 2001-83179	20010808
EP 1309721	A2	20030514	EP 2001-961958	20010808
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BR 2001013266	A	20050104	BR 2001-13266	20010808
JP 2005503102	T	20050203	JP 2002-519661	20010808
HU 2005001110	A2	20060328	HU 2005-1110	20010808
HU 2005001110	A3	20060628		
AU 2001283179	B2	20060713	AU 2001-283179	20010808
NZ 524034	A	20061130	NZ 2001-524034	20010808
NO 2003000658	A	20030409	NO 2003-658	20030210
MX 2003001218	A	20030527	MX 2003-1218	20030210
ZA 2003001109	A	20040720	ZA 2003-1109	20030210
BG 107623	A	20031128	BG 2003-107623	20030310
PRIORITY APPLN. INFO.:			US 2000-637054 A	20000811
			WO 2001-US24822 W	20010808

OTHER SOURCE(S): MARPAT 136:194260
AB Methods for identifying compds. which modulate activity of a multiple linease kinase protein and promotes cell survival or cell death comprising the steps of contacting the cell containing the multiple linease protein with the compound, determining whether the compound decreases activity of the multiple linease protein, and determining whether the compound promotes cell survival are

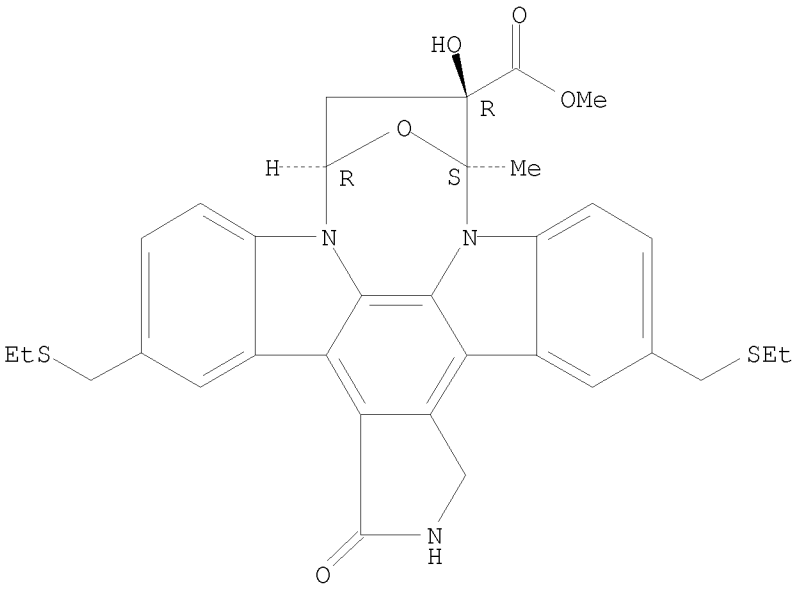
provided. Methods for identifying compds. which may be useful in the treatment of neurodegenerative disorders and/or inflammation are also provided. Methods for modulating the activity of a multiple lineage kinase protein comprising contacting the protein or a cell containing the protein with an indeno- or indolo-compound of the invention are also provided. Methods of treating neurodegenerative disorders and/or inflammation are also provided.

IT 156177-65-0
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for modulating multiple lineage kinase proteins and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

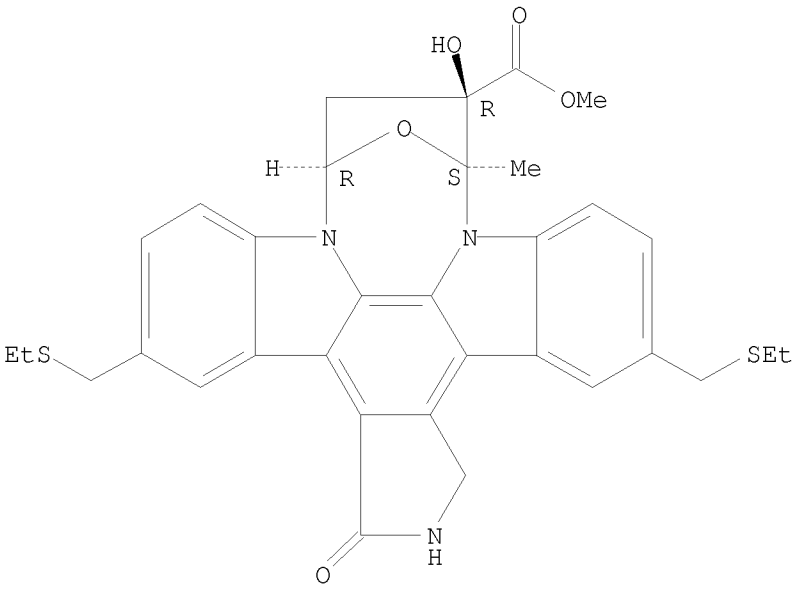
Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 43 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:45909 CAPLUS
DOCUMENT NUMBER: 136:193542
TITLE: Effects of small molecule neurotrophin mimetics on neuronal survival and regeneration in culture and in vivo
AUTHOR(S): Harper, Sarah J.
CORPORATE SOURCE: Neuroscience Research Centre, Department of Pharmacology, Merck, Sharp and Dohme Research Laboratories, Harlow, Essex, UK
SOURCE: Immunophilins in the Brain: FKBP Ligands: Novel Strategies for the Treatment of Neurodegenerative Disorders, [Proceedings from the Conference on Neuroimmunophilins], 1st, Schlangenbad, Germany, July 9-11, 1999 (2000), Meeting Date 1999, 117-127. Editor(s): Gold, Bruce G.; Fischer, Gunter; Herdegen, Thomas. Prous Science: Barcelona, Spain. CODEN: 69CEO5; ISBN: 84-8124-165-2
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review which describes the development of small mol. mimetic compds. as drug candidates. Small mol. neurotrophic factor mimetic compds. are likely to have improved pharmacokinetic properties and less side effects compared with peptide growth factors. To date, few mimetic compds. that bind directly to growth factor receptors have been identified and no agonists at the Trk receptors have been reported. The most promising candidates for mimetics include CEP-1347, which inhibits JNK signaling, immunophilin ligands, which appear to cause neuronal sprouting by an unknown mechanism, and caspase inhibitors, which may reduce cell death assocs. with neurol. disorders.
IT 156177-65-0, CEP-1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of small mol. neurotrophin mimetics on neuronal survival and regeneration in culture and in vivo)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

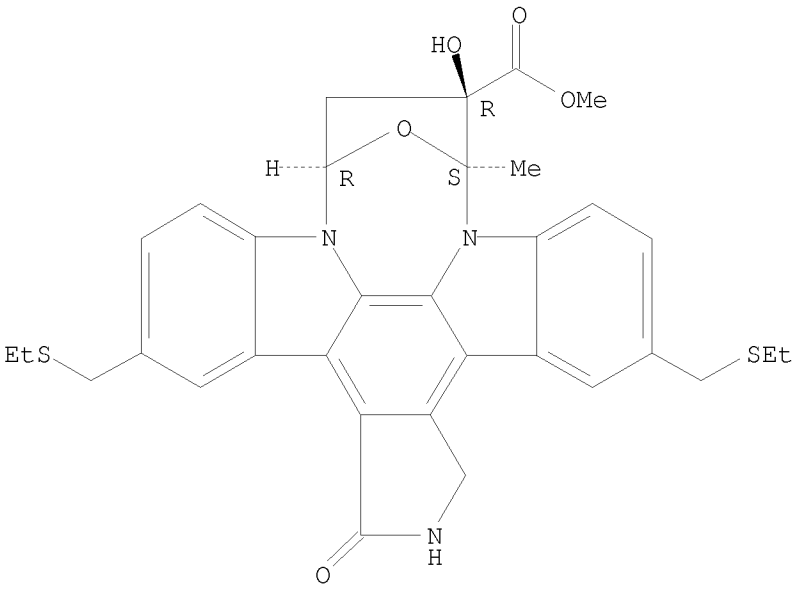
Absolute stereochemistry.



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 44 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:27143 CAPLUS
DOCUMENT NUMBER: 136:194640
TITLE: Inhibition of the c-Jun N-terminal kinase signaling pathway by the mixed lineage kinase inhibitor CEP-1347 (KT7515) preserves metabolism and growth of trophic factor-deprived neurons
AUTHOR(S): Harris, Charles A.; Deshmukh, Mohanish; Tsui-Pierchala, Brian; Maroney, Anna C.; Johnson, Eugene M., Jr.
CORPORATE SOURCE: Department of Molecular Biology and Pharmacology, Washington University, St. Louis, MO, 63110, USA
SOURCE: Journal of Neuroscience (2002), 22(1), 103-113
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nerve growth factor (NGF) deprivation triggers metabolic changes in sympathetic neurons that precede cell death. Here, we investigate the role of the c-Jun N-terminal kinase (JNK) pathway in downregulating neuronal metabolism We show that, in the presence of CEP-1347 (KT7515), a small mol. known to block cell death upstream of JNK, cellular metabolism is preserved in neurons deprived of NGF. Biochem. data that are presented are consistent with the mechanism of action of CEP-1347 being the inhibition of the mixed lineage kinases (MLKs), known activators of JNK signaling. We demonstrate that CEP-1347-saved neurons continue to grow even in the absence of NGF, indicating that inhibition of the JNK pathway is permissive for neuronal growth in the absence of trophic support. These trophic effects are seen despite the fact that CEP-1347 does not stimulate several known survival kinase pathways. In addition to blocking Bax-dependent cytochrome c release, the inhibition of the JNK signaling pathway with CEP-1347 also blocks the development of competence-to-die in response to cytosolic cytochrome c. Therefore, inhibition of the JNK signaling pathway with the MLK inhibitor CEP-1347 inhibits both limbs of the apoptotic pathway. Finally, we demonstrate that neurons that have been NGF-deprived long-term but that have been kept alive by caspase inhibitors can be rescued metabolically by CEP-1347 as assessed by soma size, cytochrome c localization, and protein synthesis rates. Therefore, we conclude that, in addition to converting extracellular signals into decisions of life and death, the JNK pathway can modulate cellular metabolism directly and thereby maintain not only survival but the "quality of life" of neurons.
IT 156177-65-0, CEP-1347
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); BIOL (Biological study); USES (Uses)
(c-Jun N-terminal kinase signaling inhibition by mixed lineage kinase inhibitor preserves metabolism and growth of trophic factor-deprived neurons)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

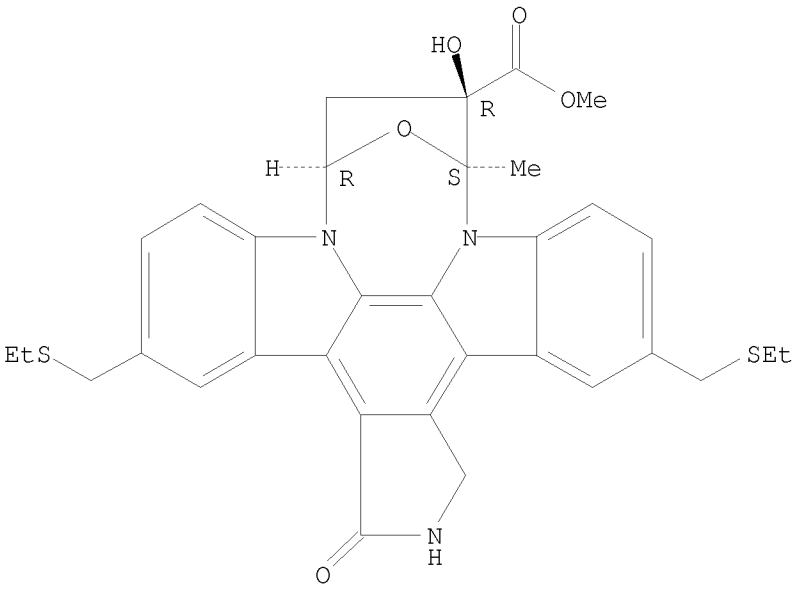
Absolute stereochemistry.



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 45 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:21235 CAPLUS
DOCUMENT NUMBER: 137:179403
TITLE: Blockade of c-Jun N-terminal kinase pathway attenuates gentamicin-induced cochlear and vestibular hair cell death
AUTHOR(S): Ylikoski, Jukka; Liang, Xing-Qun; Virkkala, Jussi; Pirvola, Ulla
CORPORATE SOURCE: Institute of Biotechnology, University of Helsinki, Helsinki, 00014, Finland
SOURCE: Hearing Research (2002), 163(1-2), 71-81
CODEN: HERED3; ISSN: 0378-5955
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The ototoxic action of aminoglycoside antibiotics leading to the loss of hair cells of the inner ear is well documented. However, the mol. mechanisms are poorly defined. The authors have previously shown that in neomycin-exposed organotypic cultures of the cochlea, the c-Jun N-terminal kinase (JNK) pathway - associated with stress, injury and apoptosis - is activated in hair cells and leads to their death. The authors have also shown that hair cell death can be attenuated by CEP-1347, an inhibitor of JNK signalling. In the present study, the authors demonstrate that gentamicin-induced ototoxicity leads to JNK activation and apoptosis in the inner ear hair cells in vivo. The authors also show that systemic administration of CEP-1347 attenuates gentamicin-induced decrease of auditory sensitivity and cochlear hair cell damage. In addition, CEP-1347 treatment reduces the extent of hair cell loss in the ampullary cristae after gentamicin intoxication. Particularly, the inner hair cells of the cochlea and type I hair cells of the vestibular organs are protected. The authors have previously shown that also acoustic overstimulation leads to apoptosis of cochlear hair cells and that CEP-1347 can attenuate noise-induced sensory cell loss. These results suggest that activation of the JNK cascade may be a common mol. outcome of cellular stress in the inner ear sensory epithelia, and that attenuation of the lesion can be provided by inhibiting JNK activation.
IT 156177-65-0, CEP-1347
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(blockade of c-JNK pathway attenuates gentamicin-induced cochlear and vestibular hair cell death)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

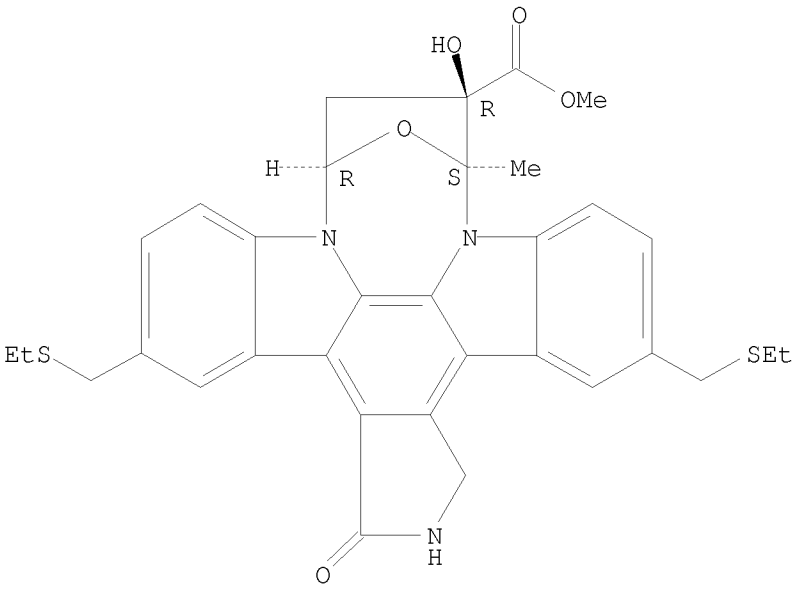
Absolute stereochemistry.



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 46 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:1465 CAPLUS
DOCUMENT NUMBER: 136:363246
TITLE: Mixed lineage kinase activity of indolocarbazole analogues
AUTHOR(S): Murakata, Chikara; Kaneko, Masami; Gessner, George; Angeles, Thelma S.; Ator, Mark A.; O'Kane, Teresa M.; McKenna, Beth Ann W.; Thomas, Beth Ann; Mathiasen, Joanne R.; Saporito, Michael S.; Bozyczko-Coyne, Donna; Hudkins, Robert L.
CORPORATE SOURCE: Kyowa-Hakko Kogyo Co., Ltd., Tokyo, Japan
SOURCE: Bioorganic & Medicinal Chemistry Letters (2002), 12(2), 147-150
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:363246
AB The MLK1-3 activity for a series of analogs of the indolocarbazole K-252a is reported. Addition of 3,9-bis-alkylthiomethyl groups to K-252a results in potent and selective MLK inhibitors. The in vitro and in vivo neuronal survival promoting activity of bis-isopropylthiomethyl-K-252a (CEP-11004/KT-8138) is reported. CEP-11004 demonstrated protection of the JNK kinase pathway following treatment of cells with MPP+ and demonstrated in vivo protection of dopaminergic terminals with the striatum projecting from neurons within the substantia nigra om mice following administration of MPTP. Thus, inhibition of MLKs may be an effective strategy for blocking neurodegeration association with Parkinson's disease.
IT 156177-65-0, CEP 1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mixed lineage kinase inhibitor activity of indolocarbazole analogs in relation to neuroprotectant activity and treatment of Parkinson's disease)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

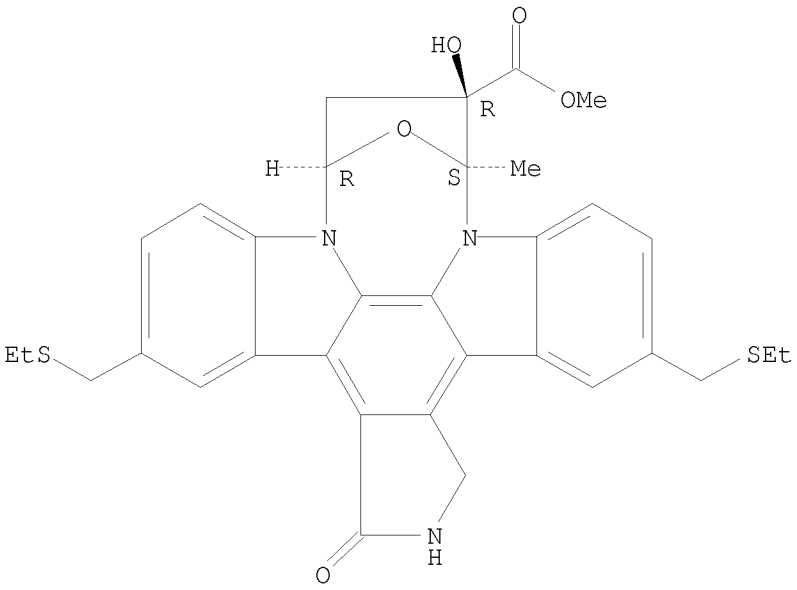
Absolute stereochemistry.



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 47 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2001:522414 CAPLUS
DOCUMENT NUMBER: 135:327235
TITLE: CEP-1347 (KT7515), a semisynthetic inhibitor of the mixed lineage kinase family
AUTHOR(S): Maroney, Anna C.; Finn, James P.; Connors, Thomas J.; Durkin, John T.; Angeles, Thelma; Gessner, George; Xu, Zhiheng; Meyer, Sheryl L.; Savage, Mary J.; Greene, Lloyd A.; Scott, Richard W.; Vaught, Jeffry L.
CORPORATE SOURCE: Cephalon Inc., West Chester, PA, 19380, USA
SOURCE: Journal of Biological Chemistry (2001), 276(27), 25302-25308
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CEP-1347 (KT7515) promotes neuronal survival at dosages that inhibit activation of the c-Jun amino-terminal kinases (JNKs) in primary embryonic cultures and differentiated PC12 cells after trophic withdrawal and in mice treated with 1-methyl-4-Ph tetrahydropyridine. In an effort to identify mol. target(s) of CEP-1347 in the JNK cascade, JNK1 and known upstream regulators of JNK1 were co-expressed in Cos-7 cells to determine whether CEP-1347 could modulate JNK1 activation. CEP-1347 blocked JNK1 activation induced by members of the mixed lineage kinase (MLK) family (MLK3, MLK2, MLK1, dual leucine zipper kinase, and leucine zipper kinase). The response was selective because CEP-1347 did not inhibit JNK1 activation in cells induced by kinases independent of the MLK cascade. CEP-1347 inhibition of recombinant MLK members in vitro was competitive with ATP, resulting in IC50 values ranging from 23 to 51 nM, comparable to inhibitory potencies observed in intact cells. In addition, overexpression of MLK3 led to death in Chinese hamster ovary cells, and CEP-1347 blocked this death at doses comparable to those that inhibited MLK3 kinase activity. These results identify MLKs as targets of CEP-1347 in the JNK signaling cascade and demonstrate that CEP-1347 can block MLK-induced cell death.
IT 156177-65-0, CEP-1347
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CEP-1347 (KT7515), a semisynthetic inhibitor of mixed lineage kinase family)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

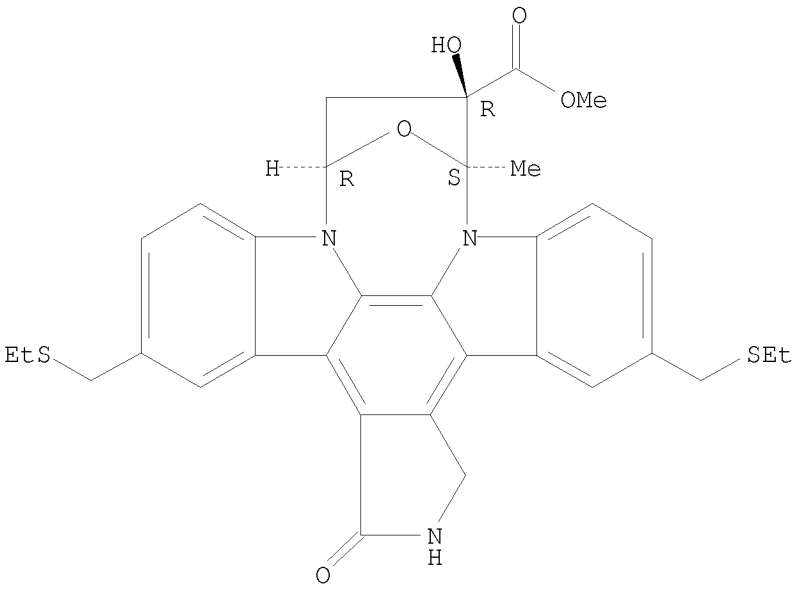
Absolute stereochemistry.



REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 48 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2001:361635 CAPLUS
DOCUMENT NUMBER: 135:205461
TITLE: CEP-1347/KT-7515, an inhibitor of SAPK/JNK pathway activation, promotes survival and blocks multiple events associated with Aβ-induced cortical neuron apoptosis
AUTHOR(S): Bozyczko-Coyne, Donna; O'Kane, Teresa M.; Wu, Zhi-Liang; Dobrzanski, Pawel; Murthy, Seetha; Vaught, Jeffry L.; Scott, Richard W.
CORPORATE SOURCE: Cephalon Inc., West Chester, PA, 19380, USA
SOURCE: Journal of Neurochemistry (2001), 77(3), 849-863
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although the mechanism of neuronal death in Alzheimer's disease (AD) has yet to be elucidated, a putative role for c-jun in this process has emerged. Thus, it was of interest to delineate signal transduction pathway(s) which regulate the transcriptional activity of c-jun, and relate these to alternate gene inductions and biochem. processes associated with beta-amyloid (Aβ) treatment. In this regard, the survival promoting activity of CEP-1347, an inhibitor of the stress-activated/c-jun N-terminal (SAPK/JNK) kinase pathway, was evaluated against Aβ-induced cortical neuron death in vitro. Moreover, CEP-1347 was used as a pharmacol. probe to associate multiple biochem. events with Aβ-induced activation of the SAPK/JNK pathway. CEP-1347 promoted survival and blocked Aβ-induced activation of JNK kinase (MKK4, also known as MEK-4, JNKK and SEK1) as well as other downstream events associated with JNK pathway activation. CEP-1347 also blocked Aβ-induction of cyclin D1 and DP5 genes and blocked Aβ-induced increases in cytoplasmic cytochrome c, caspase 3-like activity and calpain activation. The critical time window for cell death blockade by CEP-1347 resided within the peak of Aβ-induced MKK4 activation, thus defining this point as the most upstream event correlated to its survival-promoting activity. Together, these data link the SAPK/JNK pathway and multiple biochem. events associated with Aβ-induced neuronal death and further delineate the point of CEP-1347 interception within this signal transduction cascade.
IT 156177-65-0, CEP-1347
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CEP-1347/KT-7515, inhibitor of SAPK/JNK pathway activation, promotes survival and blocks multiple events associated with Aβ-induced cortical neuron apoptosis)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



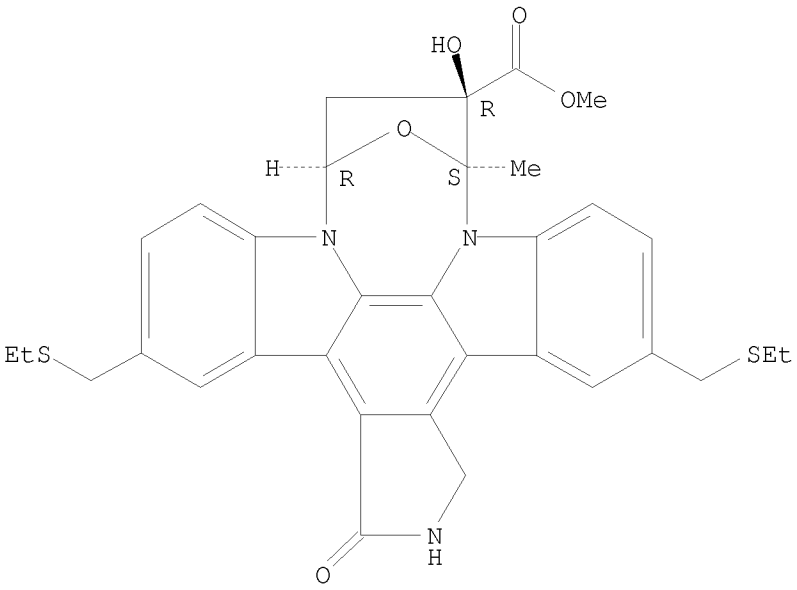
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 49 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:731495 CAPLUS
DOCUMENT NUMBER: 133:301183
TITLE: Nasal compositions containing diindolopyrrolobenzodiacinecarboxylate derivatives
INVENTOR(S): Tomoda, Hiroshi; Yamamoto, Yoshihiko; Kato, Hiromi; Nakakura, Seiji; Hayakawa, Eiji
PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000290184	A	20001017	JP 1999-95033	19990401

PRIORITY APPLN. INFO.: JP 1999-95033 19990401
OTHER SOURCE(S): MARPAT 133:301183
AB This present invention relates to nasal compns. comprising K 252A derivs. and phospholipids as solubilizers. K 252 A 5,16-bis[(ethylthio)methyl] derivative (known as CEP 1347) 3 mg was dissolved in 10 mL CHCl3/EtOH (1:1) solvent and mixed with 150 mg lysophosphatidylcholine dissolved in 10 mL CHCl3/EtOH (1:1) solvent. Water 2 mL was added to a thin membrane obtained after removal of the solvents to give a nasal preparation
IT 156177-65-0
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nasal compns. containing K 252A derivs. and solubilizers)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.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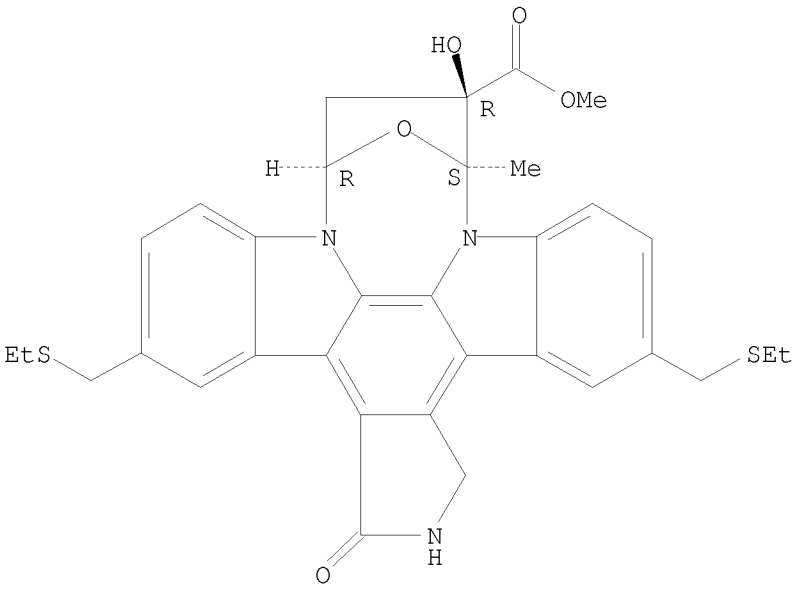
L4 ANSWER 50 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:567071 CAPLUS
DOCUMENT NUMBER: 133:276213
TITLE: CEP-1347 increases ChAT activity in culture and promotes cholinergic neurone survival following fimbria-fornix lesion
AUTHOR(S): Harper, Sarah J.; Saporito, Michael S.; Hewson, Louise; Young, Lisa; Smith, David; Rigby, Mike; Jackson, Philip; Curtis, Neil; Swain, Chris; Hefti, Franz; Vaught, L.; Sirinathsinghji, Dalip
CORPORATE SOURCE: Neuroscience Research Centre, Department of Pharmacology, Merck, Sharp and Dohme Research Laboratories, Harlow, CM20 2QR, UK
SOURCE: NeuroReport (2000), 11(10), 2271-2276
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent evidence suggests that the activation of the Jun N-terminal kinase (JNK) signal transduction pathway may be important in neuronal responses to stresses such as trophic factor deprivation. Preventing the activation of JNK and expression of c-Jun may, therefore, be neuroprotective. Here, the authors report that the small mol. CEP-1347, which has been shown to inhibit the JNK signaling pathway, promotes cholinergic activity in cultured embryonic septal neurons. In vivo, the authors have shown that CEP-1347, administered either by sub-cutaneous (s.c.) injection or by continuous infusion, is partially neuroprotective, for cholinergic neurons in the medial septum, following fimbria-fornix transection. These data suggest that small mols. such as CEP-1347 may have beneficial effects in treating neurodegenerative diseases.
IT 156177-65-0, CEP-1347
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CEP-1347 increases ChAT activity in culture and promotes septal cholinergic neuron survival following fimbria-fornix lesion in rats)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

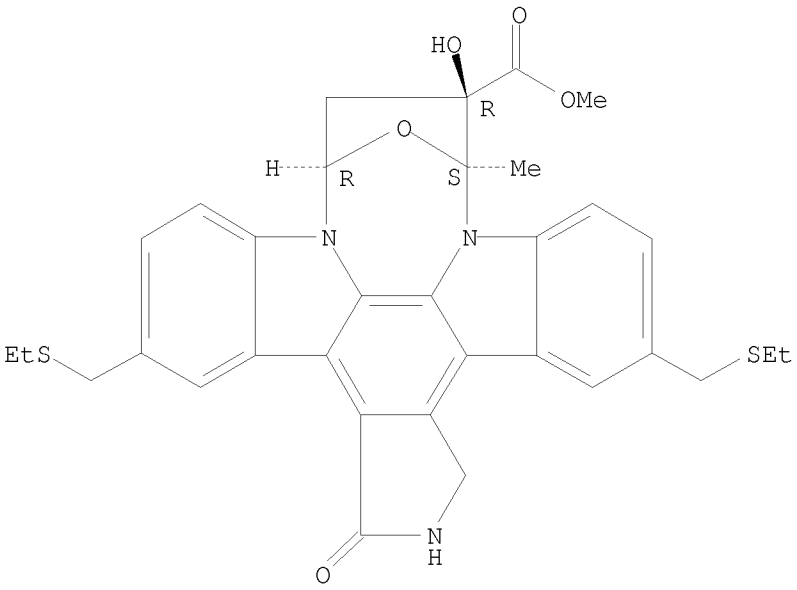
L4 ANSWER 51 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:260012 CAPLUS
DOCUMENT NUMBER: 132:260699
TITLE: Remedies for ocular diseases
INVENTOR(S): Nakata, Katsuhiko; Kageyama, Masaaki
PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan; Cephalon, Inc.
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000021531	A1	20000420	WO 1999-JP5605	19991012
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2347519	A1	20000420	CA 1999-2347519	19991012
AU 9960075	A	20000501	AU 1999-60075	19991012
EP 1121932	A1	20010808	EP 1999-970320	19991012
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NZ 511084	A	20040130	NZ 1999-511084	19991012
MX 2001003761	A	20030721	MX 2001-3761	20010411
US 6451787	B1	20020917	US 2001-807293	20010611
US 20030013701	A1	20030116	US 2002-228645	20020826
AU 2004202043	A1	20040610	AU 2004-202043	20040513

PRIORITY APPLN. INFO.:	JP 1998-290194	A	19981013
	AU 1999-60075	A3	19991012
	WO 1999-JP5605	W	19991012
	US 2001-807293	A1	20010611

OTHER SOURCE(S): MARPAT 132:260699
AB Remedies for ocular diseases contain diindolopyrrolobenzodiazocine derivs. (Markush structure given) as active ingredients. The effect of a compound of this invention in a retinal ischemia/reperfusion model was demonstrated.
IT 156177-65-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(remedy for ocular diseases)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 52 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:227509 CAPLUS
DOCUMENT NUMBER: 132:260705
TITLE: Methods using fused pyrrolocarbazole compounds for preventing/treating damage to sensory hair cells and cochlear neurons
INVENTOR(S): Ylikoski, Jukka; Pirvola, Ulla; Saarma, Mart; Walton, Kevin; Hudkins, Robert L.
PATENT ASSIGNEE(S): Cephalon, Inc., USA
SOURCE: PCT Int. Appl., 232 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000018407	A1	20000406	WO 1999-US21780		19990924
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2345295	A1	20000406	CA 1999-2345295		19990924
AU 9960532	A	20000417	AU 1999-60532		19990924
AU 763435	B2	20030724			
EP 1126855	A1	20010829	EP 1999-969678		19990924
EP 1126855	B1	20070509			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY					
JP 2002525329	T	20020813	JP 2000-571925		19990924
US 6448283	B1	20020910	US 1999-404187		19990924
NZ 511024	A	20031031	NZ 1999-511024		19990924
AT 361752	T	20070615	AT 1999-969678		19990924
CN 1329034	C	20070801	CN 1999-813612		19990924
ES 2288042	T3	20071216	ES 1999-969678		19990924
MX 2001003048	A	20020208	MX 2001-3048		20010323
US 20020115706	A1	20020822	US 2002-41224		20020108
HK 1040053	A1	20070921	HK 2002-101420		20020225
PRIORITY APPLN. INFO.:			US 1998-101763P	P	19980925
			US 1999-404187	A3	19990924
			WO 1999-US21780	W	19990924

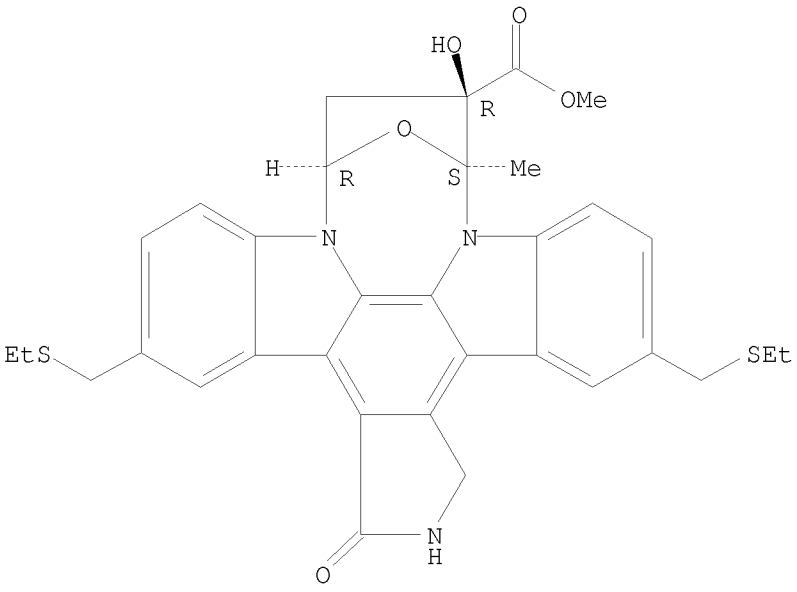
OTHER SOURCE(S): MARPAT 132:260705
AB Methods for preventing or treating damage to sensory hair cells and cochlear neurons are disclosed. The methods comprise the administration of an effective amount of a fused pyrrolocarbazole compound (Markush included). The method provides for the prevention/treatment of both hearing loss and loss of the sense of balance. Preparation of compds. of the invention is described.
IT 156177-65-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(fused pyrrolocarbazoles for preventing or treating damage to sensory hair cells and cochlear neurons)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 53 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:161543 CAPLUS
DOCUMENT NUMBER: 132:217150
TITLE: Methods for identification of compounds modulating multiple lineage kinase proteins, compound preparation, and therapeutic use
INVENTOR(S): Maroney, Anna; Walton, Kevin M.; Dionne, Craig A.; Neff, Nicola; Knight, Ernest, Jr.; Glicksman, Marcie A.
PATENT ASSIGNEE(S): Cephalon, Inc., USA
SOURCE: PCT Int. Appl., 158 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000013015	A1	20000309	WO 1999-US18864	19990818
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2339539	A1	20000309	CA 1999-2339539	19990818
AU 9956793	A	20000321	AU 1999-56793	19990818
AU 765637	B2	20030925		
EP 1105728	A1	20010613	EP 1999-943759	19990818
EP 1105728	B1	20050413		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200100589	T2	20010723	TR 2001-589	19990818
BR 9913190	A	20011211	BR 1999-13190	19990818
HU 2001003079	A2	20011228	HU 2001-3079	19990818
HU 2001003079	A3	20040301		
JP 2002523780	T	20020730	JP 2000-567949	19990818
NZ 509612	A	20031031	NZ 1999-509612	19990818
CN 1589788	A	20050309	CN 2004-10049108	19990818
AT 293254	T	20050415	AT 1999-943759	19990818
CN 1206535	C	20050615	CN 1999-810135	19990818
ES 2241316	T3	20051016	ES 1999-943759	19990818
TR 200400635	T2	20051021	TR 2004-635	19990818
CN 1879617	A	20061220	CN 2006-10099703	19990818
NO 2001000389	A	20010402	NO 2001-389	20010123
BG 105360	A	20011031	BG 2001-105360	20010319
HK 1037722	A1	20051007	HK 2001-108292	20011123

PRIORITY APPLN. INFO.:	US 1998-97980P	P	19980826
	CN 2004-10049108	A3	19990818
	WO 1999-US18864	W	19990818

OTHER SOURCE(S): MARPAT 132:217150
AB Methods for identifying compds. which modulate activity of a multiple lineage kinase protein and promotes cell survival or cell death comprise contacting the cell containing the multiple lineage kinase protein with the

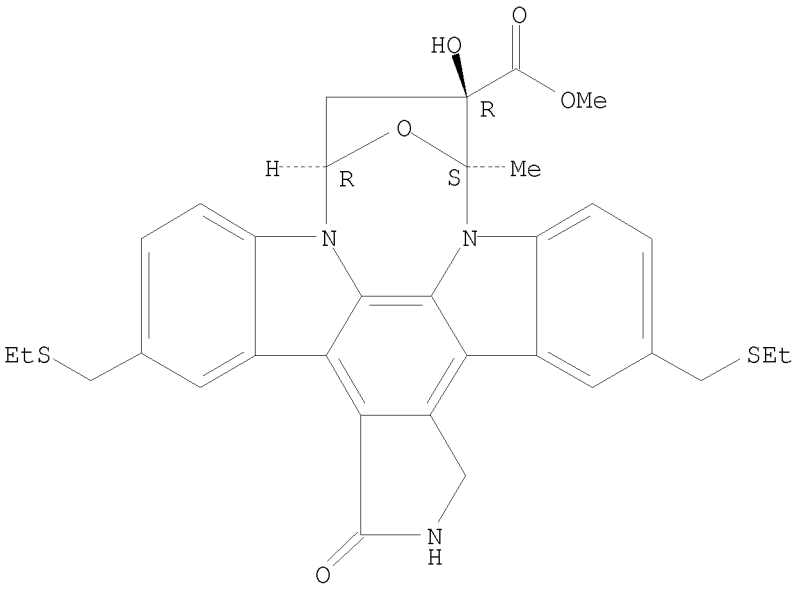
compound, determining whether the compound decreases activity of the multiple lineage kinase protein, and determining whether the compound promotes cell survival are provided. Methods for identifying compds. which may be useful in the treatment of neurodegenerative disorders and/or inflammation are also provided. Methods for modulating the activity of a multiple lineage kinase protein comprising contacting the protein or a cell containing the protein with an indeno- or indolo- compound of the invention are also provided. Methods of treating neurodegenerative disorders and/or inflammation are also provided.

IT 156177-65-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(multiple lineage kinase modulator identification, compound preparation, and therapeutic use)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

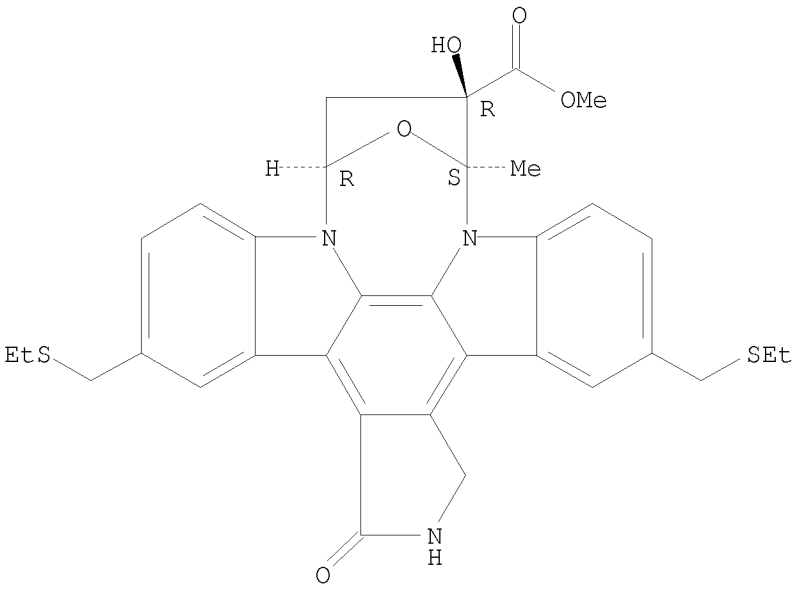
Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 54 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:125148 CAPLUS
DOCUMENT NUMBER: 132:263477
TITLE: CEP-1347 inhibits caerulein-induced rat pancreatic JNK activation and ameliorates caerulein pancreatitis
AUTHOR(S): Wagner, Andreas C. C.; Mazzucchelli, Luca; Miller, Matthew; Camoratto, Anna Marie; Goke, Burkhard
CORPORATE SOURCE: Departments of Gastroenterology, University of Bern, Bern, CH-3010, Switz.
SOURCE: American Journal of Physiology (2000), 278(1, Pt. 1), G165-G172
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Pancreatic caerulein-induced activation of c-Jun NH2-terminal kinase (JNK) has been reported, and JNK has been proposed as a mediator during induction of hyperstimulated pancreatitis. CEP-1347 has recently been described as a specific JNK inhibitor. We tested whether CEP-1347 inhibits caerulein-induced pancreatic JNK activation in isolated acini and in vivo. CEP-1347 dose dependently inhibited acinar caerulein-induced JNK activation with nearly complete inhibition at 2 μM but had no effect on digestive enzyme release. For in vivo studies, rats were pretreated with CEP-1347 before caerulein hyperstimulation. For assessment of JNK activation and histol. alterations, animals were killed 30 min or 2 and 4 h after caerulein hyperstimulation, resp. Pancreatic wet weight, serum enzyme levels, and pancreatic activity of p38 and extracellular signal-regulated kinase (ERK) were also determined Caerulein hyperstimulation strongly activated JNK, p38, and ERK. CEP-1347 pretreatment dose dependently reduced caerulein-induced pancreatic JNK activation without p38 or ERK inhibition. JNK inhibition also reduced pancreatic edema formation and reduced histol. severity of pancreatitis. Thus we show that CEP-1347 inhibits JNK activation in vivo and ameliorates caerulein-induced pancreatitis.
IT 156177-65-0, CEP-1347
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CEP-1347 inhibits caerulein-induced pancreatic JNK activation and ameliorates caerulein pancreatitis)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

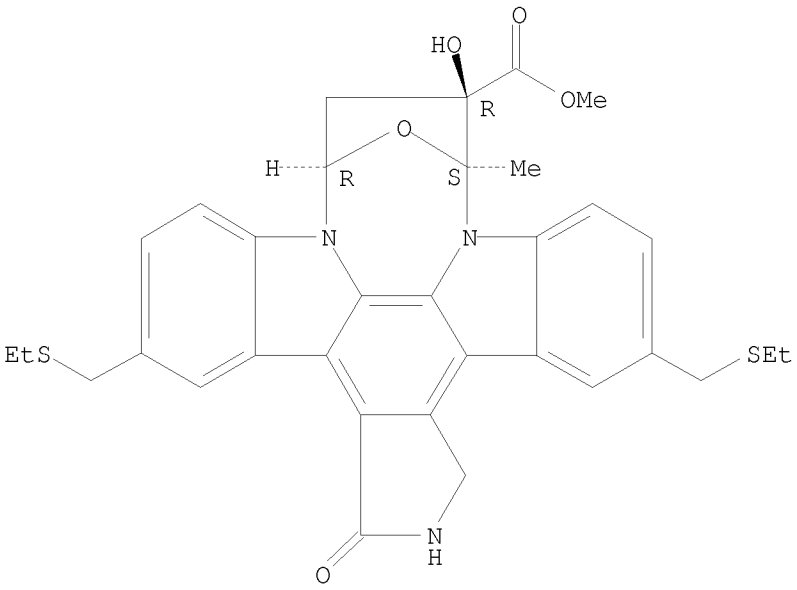
Absolute stereochemistry.



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 55 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:119174 CAPLUS
DOCUMENT NUMBER: 132:263567
TITLE: Rescue of hearing, auditory hair cells, and neurons by CEP-1347/KT7515, an inhibitor of c-Jun N-terminal kinase activation
AUTHOR(S): Pirvola, Ulla; Xing-Qun, Liang; Virkkala, Jussi; Saarma, Mart; Murakata, Chikara; Camoratto, Anna Marie; Walton, Kevin M.; Ylikoski, Jukka
CORPORATE SOURCE: Institute of Biotechnology and Department of Otorhinolaryngology, University of Helsinki, Helsinki, 00014, Finland
SOURCE: Journal of Neuroscience (2000), 20(1), 43-50
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have studied the mechanisms of auditory hair cell death after insults in vitro and in vivo. We show DNA fragmentation of hair cell nuclei after ototoxic drug and intense noise trauma. By using phospho-specific c-Jun-N-terminal kinase (JNK) and c-Jun antibodies in immunohistochem., we show that the JNK pathway, associated with stress, injury, and apoptosis, is activated in hair cells after trauma. CEP-1347, a derivative of the indolocarbazole K252a, is a small mol. that has been shown to attenuate neurodegeneration by blocking the activation of JNK. S.c. delivered CEP-1347 attenuated noise-induced hearing loss. The protective effect was demonstrated by functional tests, which showed less hearing threshold shift in CEP-1347-treated than in nontreated guinea pigs, and by morphometric methods showing less hair cell death in CEP-1347-treated cochleas. In organotypic cochlear cultures, CEP-1347 prevented neomycin-induced hair cell death. In addition to hair cells, CEP-1347 promoted survival of dissociated cochlear neurons. These results suggest that therapeutic intervention in the JNK signaling cascade, possibly by using CEP-1347, may offer opportunities to treat inner ear injuries.
IT 156177-65-0, CEP-1347
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rescue of hearing, auditory hair cells, and neurons by CEP-1347/KT7515, inhibitor of c-Jun N-terminal kinase activation, after ototoxic drug and intense noise trauma)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

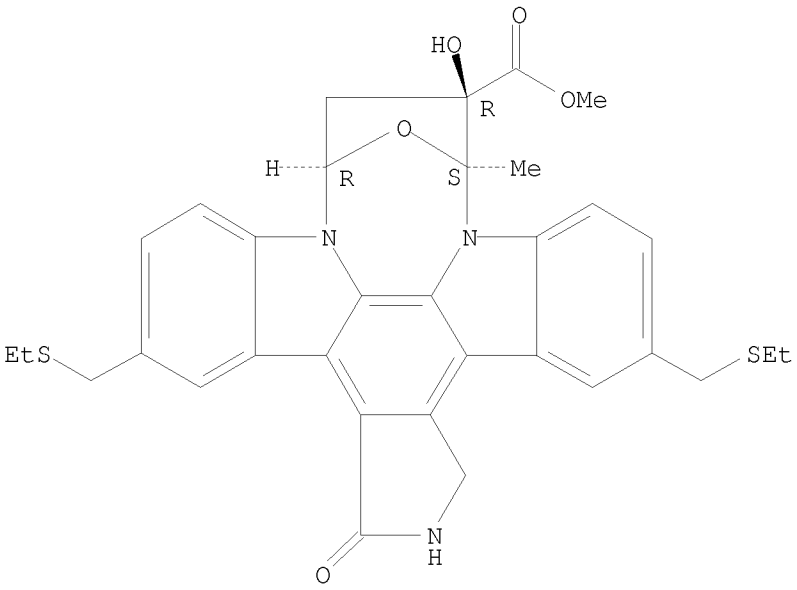
Absolute stereochemistry.



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 56 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1999:701127 CAPLUS
DOCUMENT NUMBER: 132:18728
TITLE: CEP-1347 (KT7515), an inhibitor of JNK activation, rescues sympathetic neurons and neuronally differentiated PC12 cells from death evoked by three distinct insults
AUTHOR(S): Maroney, Anna C.; Finn, James P.; Bozyczko-Coyne, Donna; O'Kane, Teresa M.; Neff, Nicola T.; Tolkovsky, Aviva M.; Park, David S.; Yan, Chao Yun Irene; Troy, Carol M.; Greene, Lloyd A.
CORPORATE SOURCE: Cephalon, West Chester, PA, 19380, USA
SOURCE: Journal of Neurochemistry (1999), 73(5), 1901-1912
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The c-Jun N-terminal kinase signaling cascade appears to play a role in some cases of cell death, including neuronal apoptosis. CEP-1347 (KT7515), an indolocarbazole of the K252a family, blocks this stress signaling cascade and promotes survival. Here, we used CEP-1347 to probe whether neuronal death pathways activated by distinct insults also possess elements in common. Cultured rat sympathetic neurons and neuronally differentiated PC12 cells were induced to die by withdrawal of nerve growth factor, exposure to UV irradiation, or subjection to oxidative stress. In each case, death was prevented by 100-200 nM CEP-1347. Moreover, in each of these death paradigms, c-Jun N-terminal kinase 1 activity in neuronally differentiated PC12 cells was elevated by two- or threefold, and this increase was totally blocked by CEP-1347 at concns. that promoted survival. In contrast, 200 nM CEP-1347 did not block death due to serum withdrawal from undifferentiated PC12 cells or to activation of Fas in Jurkat T cell cultures, even though in each case c-Jun N-terminal kinase 1 activation occurred and was inhibited by CEP-1347. These observations suggest that some but not all death pathways triggered by different insults can include a common mechanistic component, a likely candidate for which is activation of the c-Jun N-terminal kinase signaling cascade.
IT 156177-65-0, CEP-1347
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CEP-1347, as inhibitor of JNK activation, rescues sympathetic neurons and neuronally differentiated PC12 cells from death evoked by different insults)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

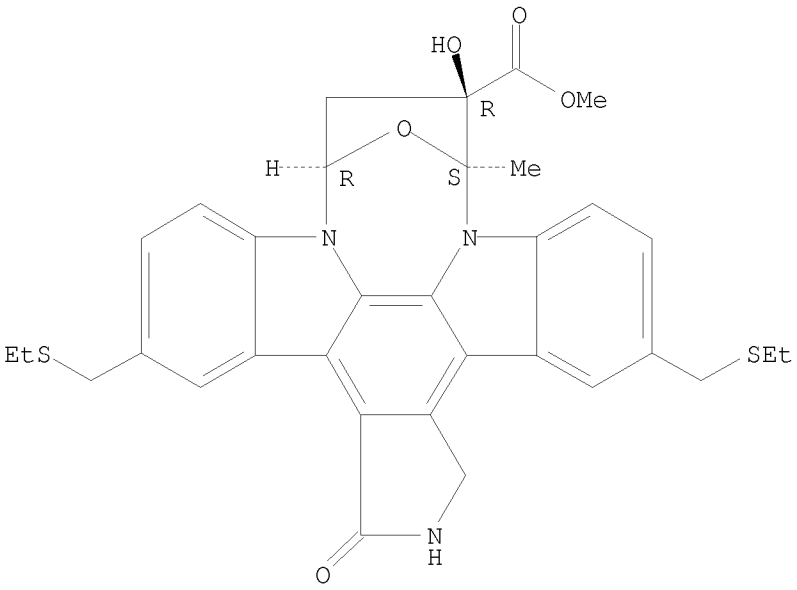
L4 ANSWER 57 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1999:99712 CAPLUS
DOCUMENT NUMBER: 130:291459
TITLE: CEP-1347/KT-7515, an inhibitor of c-jun N-terminal kinase activation, attenuates the 1-methyl-4-phenyl tetrahydropyridine-mediated loss of nigrostriatal dopaminergic neurons in vivo
AUTHOR(S): Saporito, Michael S.; Brown, Ellen M.; Miller, Matthew S.; Carswell, Susan
CORPORATE SOURCE: Cephalon Inc., West Chester, PA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1999), 288(2), 421-427
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have identified a bis-ethylthiomethyl analog of K-252a, CEP-1347/KT-7515, that promotes neuronal survival in culture and in vivo. The neuronal survival properties of CEP-1347/KT-7515 may be related to its ability to inhibit the activation of c-jun N-terminal kinase, a key kinase in some forms of stress-induced neuronal death and perhaps apoptosis. There is evidence that the selective nigrostriatal dopaminergic neurotoxin, MPTP, produces neuronal apoptosis in culture and in adult mice. Thus, our studies were designed to determine if CEP-1347/KT-7515 could protect dopaminergic neurons from MPTP-mediated neurotoxicity. CEP-1347/KT-7515 was assessed for neuroprotective activity in a low dose MPTP model (20 mg/kg) where there was a 50% loss of striatal dopaminergic terminals in the absence of substantia nigra neuronal loss, and a high dose (40 mg/kg) MPTP model where there was a complete loss of dopaminergic terminals and 80% loss of dopaminergic cell bodies. In the low dose MPTP model, CEP-1347/KT-7515 (0.3 mg/kg/day) attenuated the MPTP-mediated loss of striatal dopaminergic terminals by 50%. In the high dose model, CEP-1347/KT-7515 ameliorated the loss of dopaminergic cell bodies by 50% and partially preserved striatal dopaminergic terminals. CEP-1347/KT-7515 did not inhibit monoamine oxidase B or the dopamine transporter, suggesting that the neuroprotective effects of CEP-1347/KT-7515 occur down-stream of the metabolic conversion of MPTP to MPP+ and accumulation of MPP+ into dopaminergic neurons. These data implicate a c-jun N-terminal kinase signaling system in MPTP-mediated dopaminergic degeneration and suggest that CEP-1347/KT-7515 may have potential as a treatment for Parkinson's disease.

IT 156177-65-0, CEP-1347
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(CEP-1347 attenuates the MPTP-mediated loss of nigrostriatal dopaminergic neurons in vivo)

RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

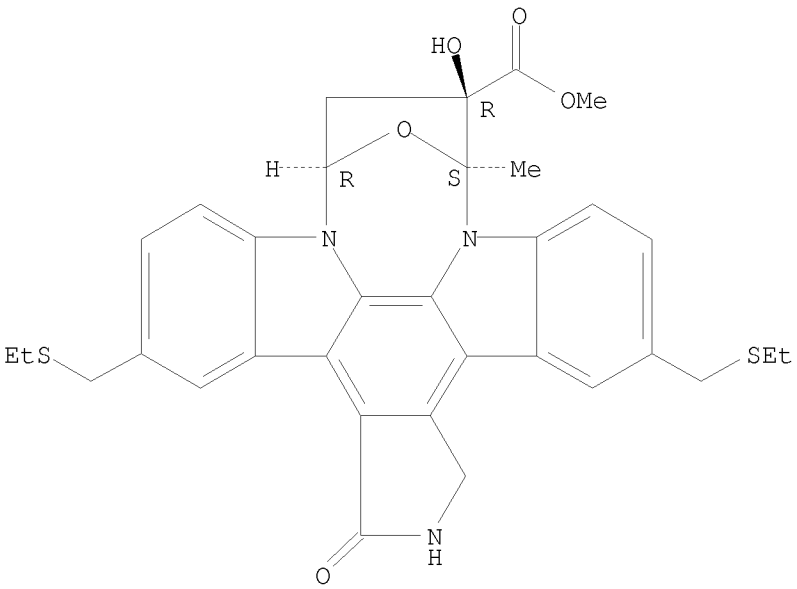
Absolute stereochemistry.



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 58 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1998:435370 CAPLUS
DOCUMENT NUMBER: 129:156863
ORIGINAL REFERENCE NO.: 129:31821a,31824a
TITLE: Chronic sparing of delayed alternation performance and choline acetyltransferase activity by CEP-1347(KT-7515) in rats with lesions of nucleus basalis magnocellularis
AUTHOR(S): Dicamillo, A. M.; Neff, N. T.; Carswell, S.; Haun, F. A.
CORPORATE SOURCE: Cephalon, Inc., West Chester, PA, 19380, USA
SOURCE: Neuroscience (Oxford) (1998), 86(2), 473-483
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Peripheral injection of the indolocarbazole CEP-1347(KT-7515) into rats that have sustained ibotenic acid lesions of the nucleus basalis magnocellularis has been shown to prevent the loss of cortically projecting neurons in that basal forebrain region. The present study tested whether this neuroprotective activity would lead to chronic sparing of a behavior known to be impaired by that lesion, as well as to chronic maintenance of cholinergic activity in cortical target regions of the nucleus basalis. CEP-1347(KT-7515) was injected into adult rats that had sustained bilateral ibotenic acid lesions of the nucleus basalis magnocellularis; the 1st injection occurred 18-24 h after lesioning, with subsequent injections of CEP-1347(KT-7515) occurring every other day over 12 days. One day following the last injection the animals were tested for retention of a previously learned delayed alternation task. Animals that received CEP-1347(KT-7515) committed significantly fewer errors than lesioned animals receiving vehicle. These same animals were tested again 8-10 wk later (10-12 wk postadministration), without receiving further drug or behavior training during the test-retest interval. The animals that had received CEP-1347(KT-7515) continued to commit fewer errors than vehicle-treated animals. Furthermore their performance at this time was indistinguishable from that of normal controls. Anal. of errors showed that CEP-1347(KT-7515) prevented a lesion-induced increase in perseverative errors, suggesting the drug improved attention in the lesioned animals. Choline acetyltransferase activity in the frontal cortex of the behaviorally tested animals that received CEP-1347(KT-7515) 3 mo previously showed a 40% recovery of the lesion-induced loss seen in the vehicle-treated animals. These results demonstrate that treatment with CEP-1347(KT-7515) over 12 days following excitotoxic damage to the nucleus basalis magnocellularis produces long-term sparing of an attention-demanding behavior.
IT 156177-65-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(sparing of delayed alternation performance and frontal cortical choline acetyltransferase activity by CEP-1347(KT-7515) in rats with lesions of nucleus basalis magnocellularis)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

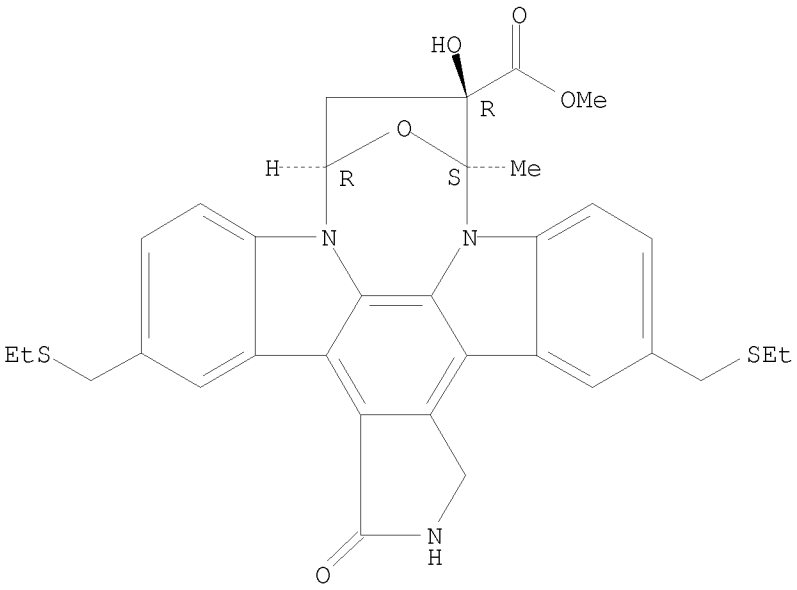
L4 ANSWER 59 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1998:435369 CAPLUS
DOCUMENT NUMBER: 129:156862
ORIGINAL REFERENCE NO.: 129:31821a,31824a
TITLE: Preservation of cholinergic activity and prevention of neuron death by CEP-1347/KT-7515 following excitotoxic injury of the nucleus basalis magnocellularis
AUTHOR(S): Saporito, M. S.; Brown, E. R.; Carswell, S.; Dicamillo, A. M.; Miller, M. S.; Murakata, C.; Neff, N. T.; Vaught, J. L.; Haun, F. A.
CORPORATE SOURCE: Cephalon Inc., West Chester, PA, 19380, USA
SOURCE: Neuroscience (Oxford) (1998), 86(2), 461-472
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have identified a class of small organic mols., derived from the indolocarbazole K-252a, that promote the survival of cultured neurons. However, many of these indolocarbazoles inhibit protein kinase C and neurotrophin-activated tyrosine kinase receptors. These kinase inhibitory activities may limit the utility of these compds. for neurol. disorders. A bis-ethyl-thiomethyl analog of K-252a, CEP-1347/KT-7515, has been identified that lacks protein kinase C and tyrosine kinase receptor inhibitory activities, yet retains the ability to promote survival of cultured neurons, including cholinergic neurons derived from the basal forebrain. In the present studies, CEP-1347/KT-7515 was assessed for neurotrophic activity on basal forebrain neurons of in vivo rats following excitotoxic insult. Ibotenate infusion into the nucleus basalis magnocellularis reduced levels of choline acetyltransferase activity in the cortex, as well as reduced nos. of choline acetyltransferase-immunoreactive and retrogradely (FluoroGold)-labeled cortically-projecting neurons in the nucleus basalis. Systemically administered CEP-1347/KT-7515 attenuated the loss of cortical choline acetyltransferase activity and the loss of the number of choline acetyltransferase-immunoreactive and retrogradely-labeled FluoroGold neurons in the nucleus basalis. Moreover, CEP-1347/KT-7515 ameliorated the loss of cortical choline acetyltransferase if administration was initiated one day, but not seven days post-lesion. Together, these results demonstrate that CEP-1347/KT-7515 protects damaged cortically-projecting basal forebrain neurons from degeneration. Thus, CEP-1347/KT-7515 may have therapeutic potential in neurodegenerative diseases, such as Alzheimer's disease, in which basal forebrain cholinergic neurons degenerate.

IT 156177-65-0, CEP 1347
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preservation of cholinergic activity and prevention of neuron death by CEP-1347/KT-7515 following excitotoxic injury of the nucleus basalis magnocellularis)

RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

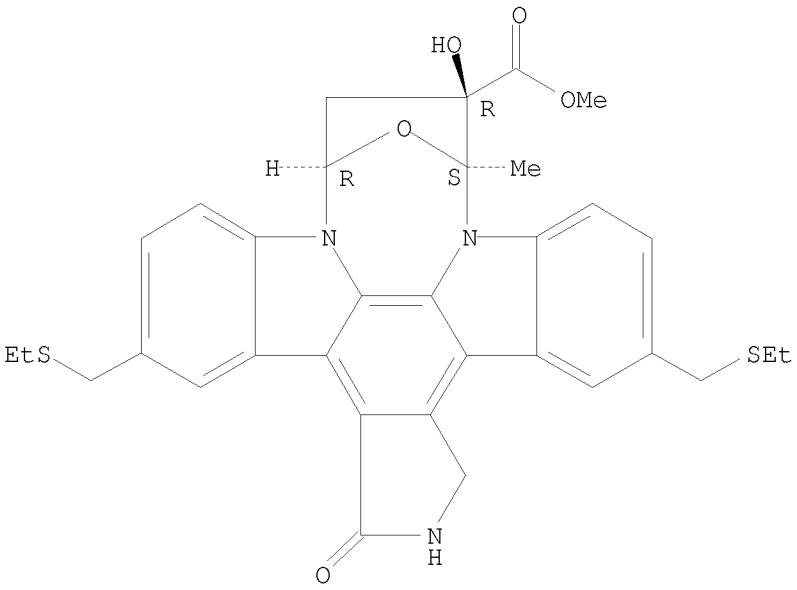
Absolute stereochemistry.



REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 60 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1998:409577 CAPLUS
DOCUMENT NUMBER: 129:187409
ORIGINAL REFERENCE NO.: 129:38037a
TITLE: CEP-1347/KT7515, a JNK pathway inhibitor, supports the in vitro survival of chick embryonic neurons
AUTHOR(S): Borasio, Gian Domenico; Horstmann, Sonja; Anneser, Johanna M. H.; Neff, Nicola T.; Glicksman, Marcie A.
CORPORATE SOURCE: Neurologische Klinik der Ludwig-Maximilians-Universitat Munchen, Klinikum Grosshadern, Munchen, D-81366, Germany
SOURCE: NeuroReport (1998), 9(7), 1435-1439
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB DEVELOPING neurons depend on target-derived trophic factors for survival in vivo and in vitro, which also decrease the activity of c-Jun N-terminal kinase (JNK). We have recently described a survival-promoting effect of inhibitors of cyclin-dependent kinases and JNK on chick peripheral embryonic neurons. Here, we report that the small trophic mol. CEP-1347/KT7515, which has been shown to inhibit the JNK signaling pathway, can promote long term-survival of cultured chick embryonic dorsal root ganglion, sympathetic, ciliary and motor neurons. Because of their pharmacol. properties, small trophic mols. such as CEP-1347/KT7515 might be of interest for the treatment of neurodegenerative disorders.
IT 156177-65-0, CEP-1347
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(CEP-1347/KT7515, a JNK pathway inhibitor, supports the in vitro survival of chick embryonic neurons)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

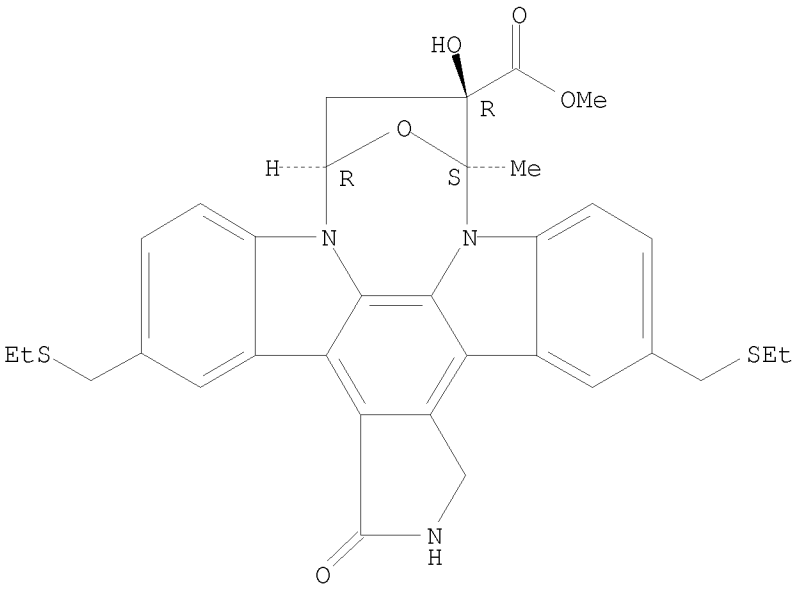
Absolute stereochemistry.



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 61 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1998:390749 CAPLUS
DOCUMENT NUMBER: 129:156808
ORIGINAL REFERENCE NO.: 129:31805a,31808a
TITLE: CEP-1347/KT7515 prevents motor neuronal programmed cell death and injury-induced dedifferentiation in vivo
AUTHOR(S): Glicksman, M. A.; Chiu, A. Y.; Dionne, C. A.; Harty, M.; Kaneko, M.; Murakata, C.; Oppenheim, R. W.; Prevette, D.; Sengelaub, D. R.; Vaught, J. L.; Neff, N. T.
CORPORATE SOURCE: Division of Neuroscience, Beckman Research Institute of the City of Hope Medical Center, Duarte, CA, 91010, USA
SOURCE: Journal of Neurobiology (1998), 35(4), 361-370
CODEN: JNEUBZ; ISSN: 0022-3034
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CEP-1347, also known as KT7515, a derivative of a natural product indolocarbazole, inhibited motor neuronal death in vitro, inhibited activation of the stress-activated kinase JNK1 (c-jun NH terminal kinase) in cultured spinal motor neurons, but had no effect on the mitogen-activated protein kinase ERK1 in these cells. Results reported here profile the functional activity of CEP-1347/KT7515 in vivo in models of motor neuronal death or differentiation. Application of CEP-1347/KT7515 to the chorioallantoic membrane of embryonic chicks rescued 40% of the lumbar motor neurons that normally die during the developmental period assessed. Peripheral administration of low doses (0.5 and 1 mg/kg daily) of CEP-1347/KT7515 reduced death of motor neurons of the spinal nucleus of the bulbocavernosus in postnatal female rats, with efficacy comparable to testosterone. Strikingly, daily administration of CEP-1347/KT7515 during the 4-day postnatal window of motor neuronal death resulted in persistent long-term motor neuronal survival in adult animals that received no addnl. CEP-1347/KT7515. In a model of adult motor neuronal dedifferentiation following axotomy, local application of CEP-1347/KT7515 to the transected hypoglossal nerve substantially reduced the loss of choline acetyl transferase immunoreactivity observed 7 days postaxotomy compared to untreated animals. Results from these expts. demonstrate that a small organic mol. that inhibits a signaling pathway associated with stress and injury also reduces neuronal death and degeneration in vivo.
IT 156177-65-0, KT7515
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CEP-1347 (KT7515) prevents motor neuronal programmed cell death and injury-induced dedifferentiation)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 62 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1998:352627 CAPLUS
DOCUMENT NUMBER: 129:54476
ORIGINAL REFERENCE NO.: 129:11361a,11364a
TITLE: Protein kinase inhibitors for treatment of neurological disorders
INVENTOR(S): Lewis, Michael E.; Kauer, James C.; Neff, Nicola; Roberts-Lewis, Jill; Murakata, Chikara; Saito, Hiromitsu; Matsuda, Yuzuru; Glicksman, Marcie A.; Kanai, Fumihiko; Kaneko, Masami
PATENT ASSIGNEE(S): Cephalon, Inc., USA; Kyowa Hakko Kogyo Co., Ltd.
SOURCE: U.S., 61 pp., Cont.-in-part of U.S. Ser. No. 329,540.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5756494	A	19980526	US 1995-456642	19950602
US 5461146	A	19951024	US 1993-96561	19930722
EP 768312	A2	19970416	EP 1996-116661	19930726
EP 768312	A3	19970604		
EP 768312	B1	20000906		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
EP 1002534	A1	20000524	EP 1999-120008	19930726
EP 1002534	B1	20050921		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
EP 1512688	A1	20050309	EP 2004-25114	19930726
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
US 5621100	A	19970415	US 1994-329540	19941026
CA 2203767	A1	19960509	CA 1995-2203767	19951004
WO 9613506	A1	19960509	WO 1995-US12965	19951004
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9539516	A	19960523	AU 1995-39516	19951004
AU 704314	B2	19990422		
EP 788501	A1	19970813	EP 1995-937391	19951004
EP 788501	B1	20020605		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
BR 9509480	A	19970930	BR 1995-9480	19951004
JP 10510514	T	19981013	JP 1996-514605	19951004
JP 3832512	B2	20061011		
EP 1125938	A1	20010822	EP 2001-110483	19951004
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV				
NZ 295871	A	20010928	NZ 1995-295871	19951004
AT 218571	T	20020615	AT 1995-937391	19951004
ES 2177665	T3	20021216	ES 1995-937391	19951004
US 5741808	A	19980421	US 1997-800383	19970214
GR 3034917	T3	20010228	GR 2000-402623	20001128

JP 2003113184	A	20030418	JP 2002-244111		20020823
JP 3723533	B2	20051207			
JP 2005170955	A	20050630	JP 2005-19891		20050127
JP 2005314429	A	20051110	JP 2005-150815		20050524
JP 2006117690	A	20060511	JP 2005-357071		20051212
PRIORITY APPLN. INFO.:			US 1992-920102	B2	19920724
			US 1993-96561	A2	19930722
			US 1994-329540	A2	19941026
			EP 1993-917337	A3	19930726
			EP 1996-116661	A3	19930726
			JP 1994-504731	A3	19930726
			US 1995-456642	A	19950602
			EP 1995-937391	A3	19951004
			JP 1996-514605	A3	19951004
			WO 1995-US12965	W	19951004
			EP 1999-120008	A3	19991014
			JP 2002-244111	A3	20020823

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

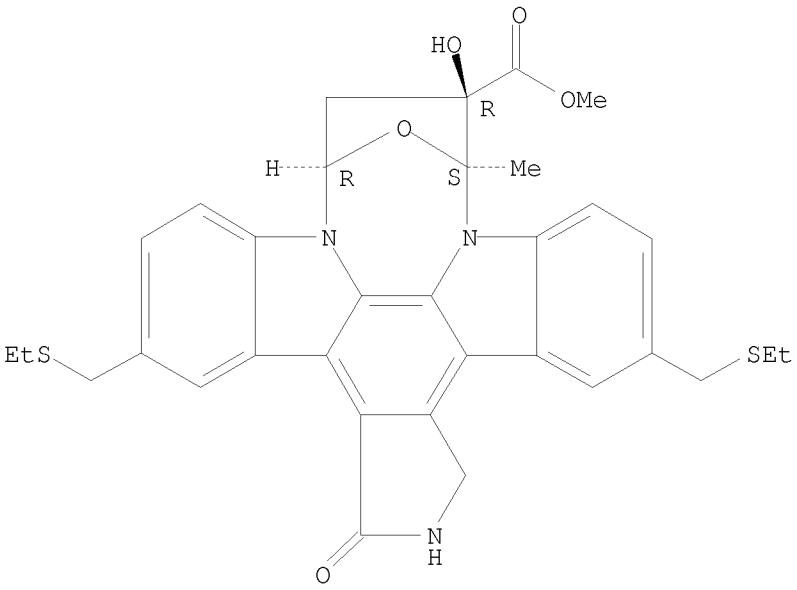
AB Derivs. of K-252a I (R = HO, MeO; R1 = H, Br, NHCONHPh, CH2SPh, 2-pyrimidinylthiomethyl, 2-furylmethylthiomethyl, etc.; R2 = H, Br, Cl, CH2OH, etc.; R 3 = CH2OH, CO2Me, CH2NHCO2Ph, CONHPh, CH2NHCO2Me, etc.; Z = O, H2), as well as novel bis-N-substituted derivs. of staurosporine XNMeWNMeX (W = C(:Y)NH, W1NHC(:Y); W1 = hydrocarbylene radical of 2-20 carbon atoms; Y = O, S) were prepared The invention also features a method for treating diseased neuronal cells involving the administration of either the novel staurosporine derivs. or specified functional derivs. of K-252a. Thus, staurosporine was treated with hexamethyl-bis-isocyanate to give 1,6-hexamethylene-bis-(carbamylstaurosporine). The spinal cord choline acetyltransferase (CHAT) activity of I (R = OH, R1 = R2 = Br; R3 = CH2OH, Z = H2) at 300 nM was 146 compared with K-252a of 100.

IT 156177-65-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of staurosporine and K-252a derivs. as protein kinase inhibitors for treatment of neurol. disorders)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 63 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1998:42283 CAPLUS
DOCUMENT NUMBER: 128:110888
ORIGINAL REFERENCE NO.: 128:21621a
TITLE: Use of K-252a derivative for the treatment of peripheral or central nerve disorders, and cytokine overproduction
INVENTOR(S): Engber, Thomas M.; Haun, Forrest A.; Saporito, Michael S.; Aimone, Lisa D.; Miller, Matthew S.; Knight, Ernest, Jr.
PATENT ASSIGNEE(S): Cephalon, Inc., USA; Engber, Thomas M.; Haun, Forrest A.; Saporito, Michael S.; Aimone, Lisa D.; Miller, Matthew S.; Knight, Ernest, Jr.
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9749406	A1	19971231	WO 1997-US10898	19970624
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2258662	A1	19971231	CA 1997-2258662	19970624
CA 2258662	C	20070206		
AU 9734090	A	19980114	AU 1997-34090	19970624
AU 721942	B2	20000720		
EP 912184	A1	19990506	EP 1997-930203	19970624
EP 912184	B1	20020925		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
CN 1228024	A	19990908	CN 1997-197341	19970624
CN 1108799	C	20030521		
BR 9710693	A	20000111	BR 1997-10693	19970624
JP 2000514420	T	20001031	JP 1998-503444	19970624
US 6184217	B1	20010206	US 1997-881679	19970624
RU 2183959	C2	20020627	RU 1999-101117	19970624
AT 224718	T	20021015	AT 1997-930203	19970624
ES 2184106	T3	20030401	ES 1997-930203	19970624
NO 9806111	A	19990223	NO 1998-6111	19981223
NO 317335	B1	20041011		
KR 2000022217	A	20000425	KR 1998-710637	19981224
HK 1018745	A1	20030117	HK 1999-103811	19990902
JP 2008189676	A	20080821	JP 2008-53174	20080304

PRIORITY APPLN. INFO.:
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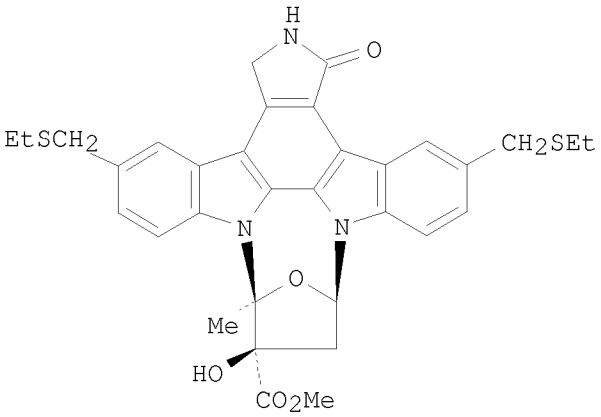
JP 1998-503444 A3 19970624
WO 1997-US10898 W 19970624

GI



I

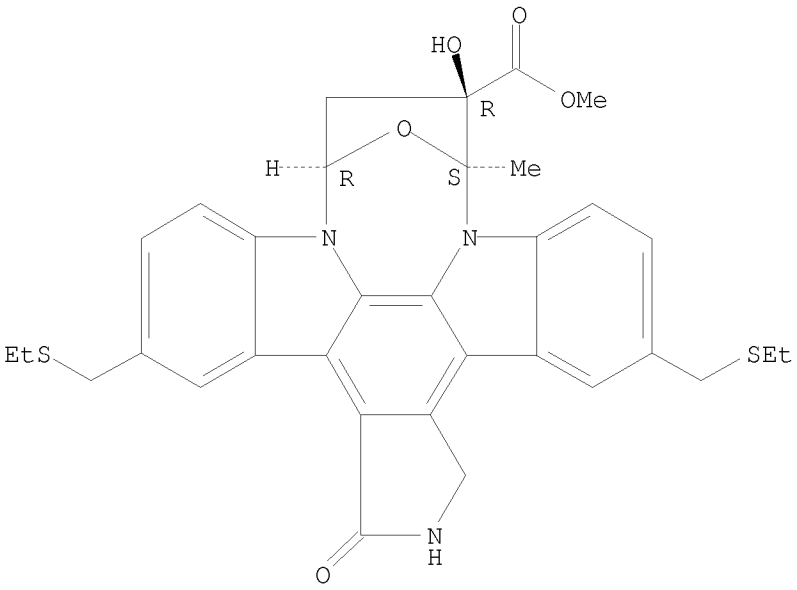
AB Therapeutic methodologies are disclosed which use a ring-substituted derivative (I) of the indolocarbazole K-252a. I is useful for treating peripheral neuropathies, central neuronal degeneration and cytokine overprodn. Typical diseases related to the above are peripheral neuropathy, Alzheimer's disease, Parkinson's disease and autoimmune and allergic conditions.

IT 156177-65-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(K-252a derivative for treatment of peripheral or central nerve disorders and cytokine overprodn.)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

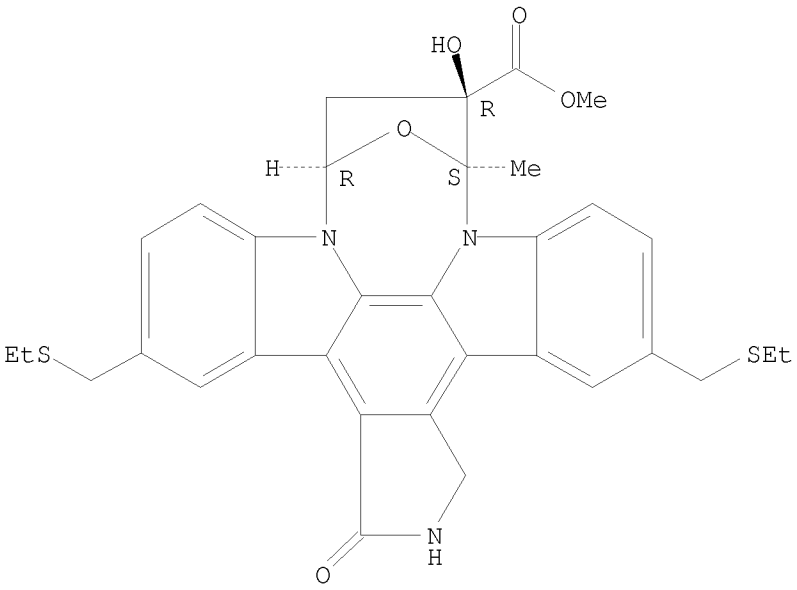
Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 64 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1998:30688 CAPLUS
DOCUMENT NUMBER: 128:152250
ORIGINAL REFERENCE NO.: 128:29945a,29948a
TITLE: Motoneuron apoptosis is blocked by CEP-1347 (KT 7515), a novel inhibitor of the JNK signaling pathway
AUTHOR(S): Maroney, Anna C.; Glicksman, Marcie A.; Basma, Alie N.; Walton, Kevin M.; Knight, Ernest, Jr.; Murphy, Carol A.; Bartlett, Becky A.; Finn, James P.; Angeles, Theima; Matsuda, Yuzuru; Neff, Nicola T.; Dionne, Craig A.
CORPORATE SOURCE: Cephalon Incorporated, West Chestor, PA, 19380, USA
SOURCE: Journal of Neuroscience (1998), 18(1), 104-111
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Neurons undergoing apoptosis can be rescued by trophic factors that simultaneously increase the activity of extracellular signal-regulated kinase (ERK) and decrease c-Jun N-terminal kinase (JNK) and p38. We identified a mol., CEP-1347 (KT7515), that rescues motoneurons undergoing apoptosis and investigated its effect on ERK1 and JNK1 activity. Cultured rat embryonic motoneurons, in the absence of trophic factor, began to die 24-48 h after plating. During the first 24 h ERK1 activity was unchanged, whereas JNK1 activity increased four-fold. CEP-1347 completely rescued motoneurons for at least 72 h with an EC50 of 20 ± 2 nM. CEP-1347 did not alter ERK1 activity but rapidly inhibited JNK1 activation. The IC50 of CEP-1347 for JNK1 activation was the same as the EC50 for motoneuron survival. Inhibition of JNK1 activation by CEP-1347 was not selective to motoneurons. CEP-1347 also inhibited JNK1 activity in Cos7 cells under conditions of UV irradiation, osmotic shock, and inhibition of glycosylation. Inhibition by CEP-1347 of the JNK1 signaling pathway appeared to be selective, because CEP-1347 did not inhibit p38-regulated mitogen-activated protein kinase-activated protein kinase-2 (MAPKAP2) activity in Cos7 cells subjected to osmotic shock. The direct mol. target of CEP-1347 was not JNK1, because CEP-1347 did not inhibit JNK1 activity in Cos7 cells contransfected with MEKK1 and JNK1 cDNA constructs. This is the first demonstration of a small organic mol. that promotes motoneuron survival and that simultaneously inhibits the JNK1 signaling cascade.
IT 156177-65-0, KT 7515
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(motoneuron apoptosis is blocked by CEP-1347 (KT 7515), a novel inhibitor of the JNK signaling pathway)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

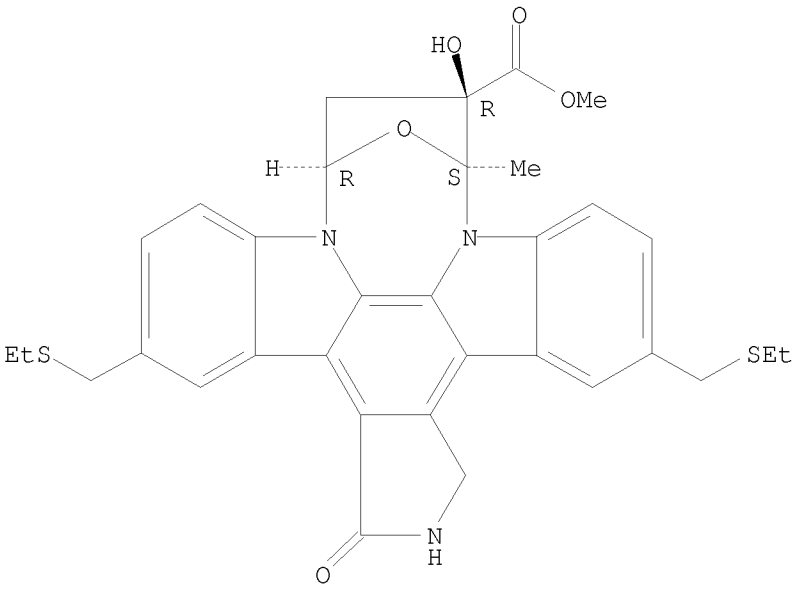
Absolute stereochemistry.



REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 65 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1997:318286 CAPLUS
DOCUMENT NUMBER: 127:262
ORIGINAL REFERENCE NO.: 127:51a
TITLE: Neurotrophic 3,9-Bis[(alkylthio)methyl]- and -Bis(alkoxymethyl)-K-252a Derivatives
AUTHOR(S): Kaneko, Masami; Saito, Yutaka; Saito, Hiromitsu; Matsumoto, Tadashi; Matsuda, Yuzuru; Vaught, Jeffry L.; Dionne, Craig A.; Angeles, Thelma S.; Glicksman, Marcie A.; Neff, Nicola T.; Rotella, David P.; Kauer, James C.; Mallamo, John P.; Hudkins, Robert L.; Murakata, Chikara
CORPORATE SOURCE: Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co. Ltd., Shizuoka, 411, Japan
SOURCE: Journal of Medicinal Chemistry (1997), 40(12), 1863-1869
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of 3,9-disubstituted [(alkylthio)methyl]- and (alkoxymethyl)-K-252a derivs. was synthesized with the aim of enhancing and separating the neurotrophic properties from the undesirable NGF (trk A kinase) and PKC inhibitory activities of K-252a. Data from this series reveal that substitution in the 3- and 9-positions of K-252a with these groups reduces trk A kinase inhibitory properties approx. 100- to >500-fold while maintaining or in certain cases enhancing the neurotrophic activity. From this research, 3,9-bis[(ethylthio)methyl]-K-252a (8) was identified as a potent and selective neurotrophic agent in vitro as measured by enhancement of choline acetyltransferase activity in embryonic rat spinal cord and basal forebrain cultures. Compound 8 was found to have weak kinase inhibitory activity for trk A, protein kinase C, protein kinase A, and myosin light chain kinase. On the basis of the in vitro profile, 8 was evaluated in in vivo models suggestive of neurol. diseases. Compound 8 was active in preventing degeneration of cholinergic neurons of the nucleus basalis magnocellularis (NBM) and reduced developmentally programmed cell death (PCD) of female rat spinal nucleus of the bulbocavernosus motoneurons and embryonic chick lumbar motoneurons.
IT 156177-65-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and neurotrophic activity of derivs. of indolocarbazole alkaloid K252a)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



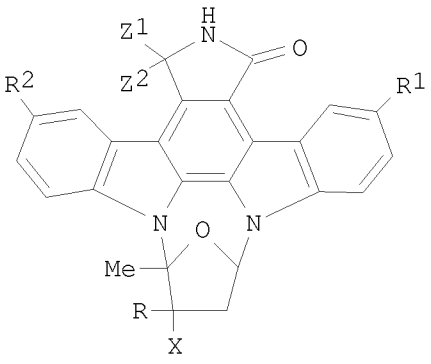
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 66 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1997:276796 CAPLUS
DOCUMENT NUMBER: 126:343709
ORIGINAL REFERENCE NO.: 126:66849a,66852a
TITLE: Protein kinase inhibitors for treatment of neurological disorders
INVENTOR(S): Lewis, Michael E.; Kauer, James C.; Neff, Nicola; Roberts-Lewis, Jill; Murakata, Chikara; Saito, Hiromitsu; Matsuda, Yuzuru; Glicksman, Marcie A.; Kanai, Fumihiko; Kaneko, Masami
PATENT ASSIGNEE(S): Cephalon, Inc., USA; Kyowa Hakko Kogyo Co., Ltd.
SOURCE: U.S., 60 pp., Cont.-in-part of U.S. 5,621,100.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5621101	A	19970415	US 1995-486739	19950607
US 5461146	A	19951024	US 1993-96561	19930722
EP 768312	A2	19970416	EP 1996-116661	19930726
EP 768312	A3	19970604		
EP 768312	B1	20000906		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
EP 1002534	A1	20000524	EP 1999-120008	19930726
EP 1002534	B1	20050921		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
EP 1512688	A1	20050309	EP 2004-25114	19930726
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
US 5621100	A	19970415	US 1994-329540	19941026
GR 3034917	T3	20010228	GR 2000-402623	20001128
JP 2003113184	A	20030418	JP 2002-244111	20020823
JP 3723533	B2	20051207		
JP 2005170955	A	20050630	JP 2005-19891	20050127

PRIORITY APPLN. INFO.:
US 1992-920102 B2 19920724
US 1993-96561 A2 19930722
US 1994-329540 A2 19941026
EP 1993-917337 A3 19930726
EP 1996-116661 A3 19930726
JP 1994-504731 A3 19930726
EP 1999-120008 A3 19991014
JP 2002-244111 A3 20020823

OTHER SOURCE(S): MARPAT 126:343709
GI



I

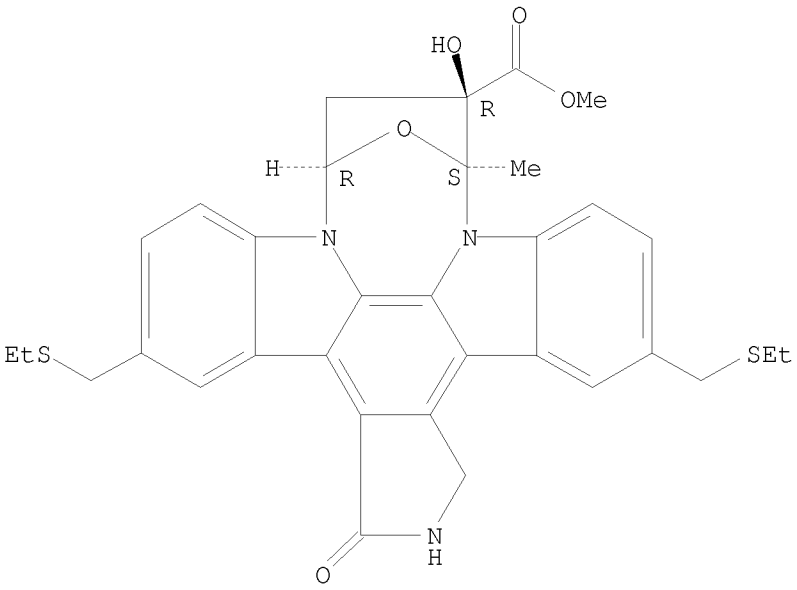
AB K-252a derivs., e.g. I [R = OH; R1 = H, CH2SO2Et, CH2SCH2CH2NH2, (1,3,5-triazol-1-yl)iminomethyl, CH2SCH2CH2NHBu, CH2CH2CH2NMe2, CH2NMe2, 2-pyridylthiomethyl, 2-pyrimidinylthiomethyl, 2-pyrimidinylsulfinylmethyl; R2 = Z1 = Z2 = H; X = CH2NHCOCH(CH2OH)NHCbz-(S), CO2Me, CONH2], were prepared as protein kinase inhibitors for treatment of neurol. disorders. I [R = OH, R1 = CH2SO2Et, R2 = Z1 = Z2 = H, X = CO2Me; (II)] was prepared from I (R = OH, R1 = CH2SEt, R2 = Z1 = Z2 = H, X = CO2Me) via oxidation with 3-ClC6H4CO3H in CHCl3. II at 30 nM had an Ipsi/Contra ratio of 62 for cortical ChAT activity in NBM rats with lesions.

IT 156177-65-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of K-252a derivs. as protein kinase inhibitors for treatment of neurol. disorders)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 67 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1997:276795 CAPLUS
DOCUMENT NUMBER: 126:343708
ORIGINAL REFERENCE NO.: 126:66849a,66852a
TITLE: K-252a derivatives for treatment of neurological disorders
INVENTOR(S): Saito, Hiromitsu; Matsuda, Yuzuru; Glicksman, Marcie A.; Kanai, Fumihiko; Kaneko, Masami; Lewis, Michael E.; Kauer, James C.; Neff, Nicola; Roberts-Lewis, Jill; Murakata, Chikara
PATENT ASSIGNEE(S): Cephalon, Inc., USA; Kyowa Hakko Kogyo Co., Ltd.
SOURCE: U.S., 51 pp., Cont.-in-part of U.S. 5,461,146.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5621100	A	19970415	US 1994-329540	19941026
US 5461146	A	19951024	US 1993-96561	19930722
EP 768312	A2	19970416	EP 1996-116661	19930726
EP 768312	A3	19970604		
EP 768312	B1	20000906		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
EP 1002534	A1	20000524	EP 1999-120008	19930726
EP 1002534	B1	20050921		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
EP 1512688	A1	20050309	EP 2004-25114	19930726
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
US 5756494	A	19980526	US 1995-456642	19950602
US 5621101	A	19970415	US 1995-486739	19950607
CA 2203767	A1	19960509	CA 1995-2203767	19951004
WO 9613506	A1	19960509	WO 1995-US12965	19951004
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9539516	A	19960523	AU 1995-39516	19951004
AU 704314	B2	19990422		
EP 788501	A1	19970813	EP 1995-937391	19951004
EP 788501	B1	20020605		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
BR 9509480	A	19970930	BR 1995-9480	19951004
JP 10510514	T	19981013	JP 1996-514605	19951004
JP 3832512	B2	20061011		
EP 1125938	A1	20010822	EP 2001-110483	19951004
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV				
NZ 295871	A	20010928	NZ 1995-295871	19951004
AT 218571	T	20020615	AT 1995-937391	19951004
ES 2177665	T3	20021216	ES 1995-937391	19951004
US 5741808	A	19980421	US 1997-800383	19970214

GR 3034917	T3	20010228	GR 2000-402623		20001128
JP 2003113184	A	20030418	JP 2002-244111		20020823
JP 3723533	B2	20051207			
JP 2005170955	A	20050630	JP 2005-19891		20050127
JP 2005314429	A	20051110	JP 2005-150815		20050524
JP 2006117690	A	20060511	JP 2005-357071		20051212
PRIORITY APPLN. INFO.:			US 1992-920102	B2	19920724
			US 1993-96561	A2	19930722
			EP 1993-917337	A3	19930726
			EP 1996-116661	A3	19930726
			JP 1994-504731	A3	19930726
			US 1994-329540	A2	19941026
			US 1995-456642	A	19950602
			EP 1995-937391	A3	19951004
			JP 1996-514605	A3	19951004
			WO 1995-US12965	W	19951004
			EP 1999-120008	A3	19991014
			JP 2002-244111	A3	20020823

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

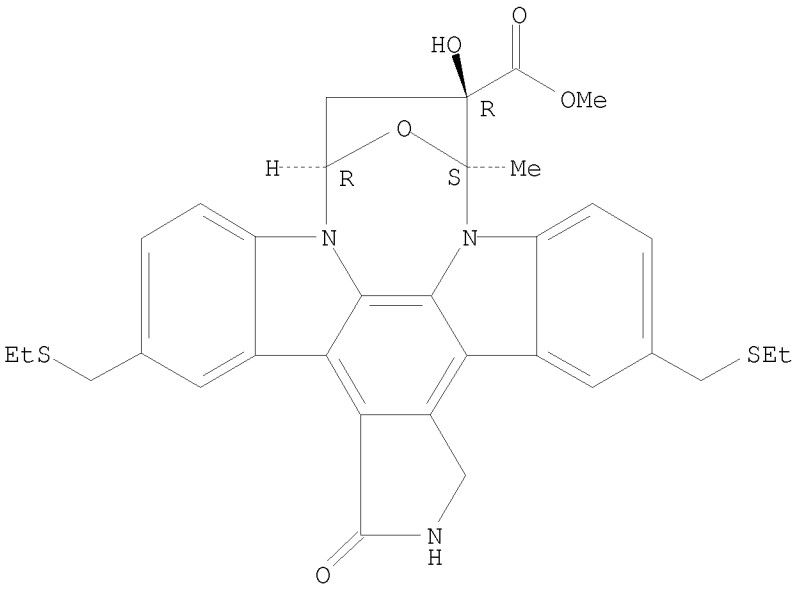
AB K-252a derivs. were prepared as agents for treatment of neurol. disorders. The derivative I is claimed. I was prepared from from dialdehyde II via reduction with NaBH4, thiolation with EtSH in the presence of CSA, and deacetylation with NaOMe. I (0.03 mg/kg QOD) had an Ipsi/Contra ratio of 93.8 for cortical ChAT activity in NBM rats with lesions.

IT 156177-65-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of K-252a derivs. as protein kinase inhibitors for treatment of neurol. disorders)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

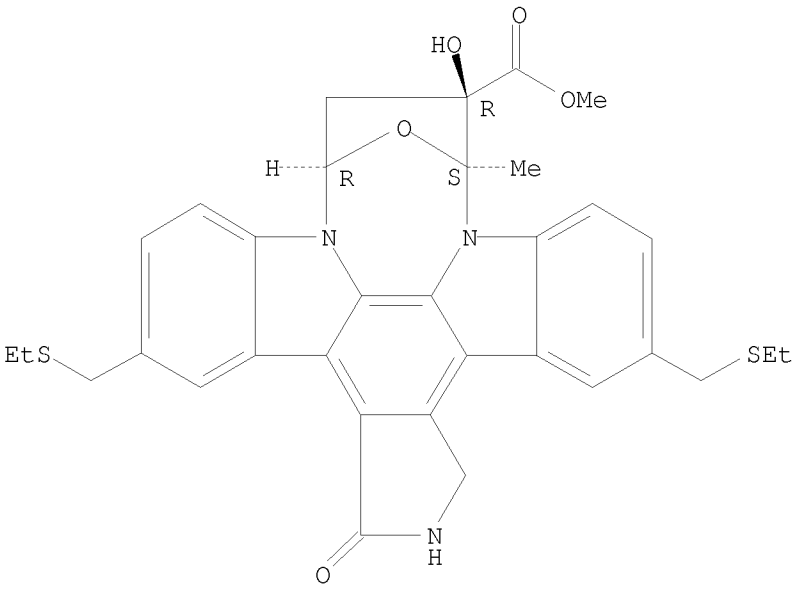
Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 68 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1997:132175 CAPLUS
DOCUMENT NUMBER: 126:207047
ORIGINAL REFERENCE NO.: 126:39881a,39884a
TITLE: In quest of lead compounds for novel pharmaceutical drugs
AUTHOR(S): Matsuda, Yuzuru
CORPORATE SOURCE: Tokyo Res. Lab., Kyowa Hakko Kogyo Co., Ltd., Machida, 194, Japan
SOURCE: Yuki Gosei Kagaku Kyokaishi (1997), 55(2), 152-158
CODEN: YGKKAE; ISSN: 0037-9980
PUBLISHER: Yuki Gosei Kagaku Kyokai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 19 refs., on the discovery of K-252a by microorganism screening, functions and action mechanisms of K-252a and its derivs., and development of new drugs (KT7515 and KT8391) from K-252a. K-252a was found as a calmodulin inhibitor, and showed protein kinase C inhibiting activity as well. The authors found that K-252a was also an NGF inhibitor, but surprisingly it showed neurotrophic factor-like activity. KT7515 shows neurotrophic activity but does not inhibit protein kinases, and it is possibly useful for the treatment of Alzheimer's disease and amyotrophic lateral sclerosis.
IT 156177-65-0, KT 7515
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(K-252a as a lead compound for development of drugs for neurodegenerative diseases)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.


HO
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L4 ANSWER 69 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1997:124905 CAPLUS
DOCUMENT NUMBER: 126:216650
ORIGINAL REFERENCE NO.: 126:41815a,41818a
TITLE: Aqueous polyethylene glycol solutions containing indolocarbazoles
INVENTOR(S): Goldstein, Joel D.; Herman, Joseph L.
PATENT ASSIGNEE(S): Cephalon, Inc., USA
SOURCE: U.S., 31 pp., Cont.-in-part of U.S. Ser. No. 199,390, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5599808	A	19970204	US 1995-383414	19950203
PRIORITY APPLN. INFO.:			US 1994-199390 B2	19940218

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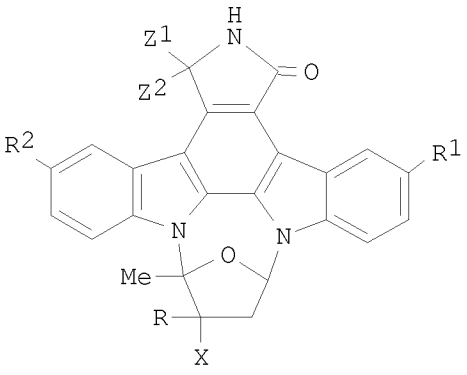
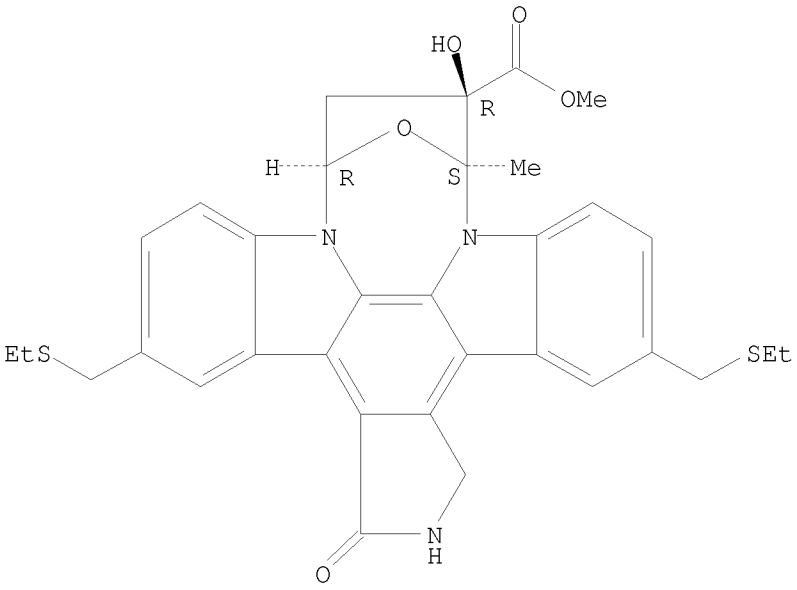


I

AB Solns. of indolocarbazoles, such as I [R = OH, OMe; R1 = H, Br, Cl, Me, NHCONHPh, CH2S(O)nEt, NMe2, NHCO2Me, CH2OCONHEt, CH2OEt, CH2NMe2, CH2SEt, CH:NNH; R2 = H, Br, Cl, NHCONHEt, CH2SEt, CH2OH; X = H, CH2N3, CO2Me, CH2OH, CONHEt, CONH2, CONHPr,CH2S(O)Me, CH:NOH, CONHCH2CH2OH, CH:NNHCONH2, CH2OAc, CONHPh, CH2S(O)nPh; Z1 = Z2 = H; Z1Z2 = O; n = 0-2], contain 1-99% organic solvent, 0.25-10% dispersant, 0-99% H2O and 0-60% polyethylene glycol. Thus, K-252a was dissolved in a solvent containing 50% PEG-600, 2% benzyl alc., 10% Triton X-100 and 38% H2O to give a solution containing 10 mg/mL
K-252a. Many I were also prepared
IT 156177-65-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of aqueous polyethylene glycol solns. containing indolocarbazoles)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-

i][1,6]benzodiazocine-10-carboxylic acid,
5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



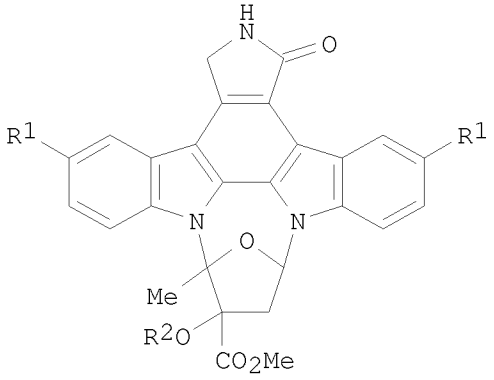
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 70 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1996:404877 CAPLUS
DOCUMENT NUMBER: 125:86967
ORIGINAL REFERENCE NO.: 125:16421a,16424a
TITLE: Protein kinase inhibitors for treatment of neurological disorders
INVENTOR(S): Lewis, Michael E.; Kauer, James C.; Neff, Nicola; Glicksman, Marcie; Roberts-Lewis, Jill; Murakata, Chikara; Saito, Hiromitsu; Matsuda, Yuzuru; Kanai, Fumihiko; Kaneko, Masami
PATENT ASSIGNEE(S): Cephalon, Inc., USA; Kyowa Hakko Kogyo Co., Ltd.
SOURCE: PCT Int. Appl., 162 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9613506	A1	19960509	WO 1995-US12965	19951004
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5621100	A	19970415	US 1994-329540	19941026
US 5756494	A	19980526	US 1995-456642	19950602
AU 9539516	A	19960523	AU 1995-39516	19951004
AU 704314	B2	19990422		
EP 788501	A1	19970813	EP 1995-937391	19951004
EP 788501	B1	20020605		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
BR 9509480	A	19970930	BR 1995-9480	19951004
JP 10510514	T	19981013	JP 1996-514605	19951004
JP 3832512	B2	20061011		
NZ 295871	A	20010928	NZ 1995-295871	19951004
AT 218571	T	20020615	AT 1995-937391	19951004

PRIORITY APPLN. INFO.:	US 1994-329540	A	19941026
	US 1995-456642	A	19950602
	US 1992-920102	B2	19920724
	US 1993-96561	A2	19930722
	WO 1995-US12965	W	19951004

OTHER SOURCE(S): MARPAT 125:86967
GI



I

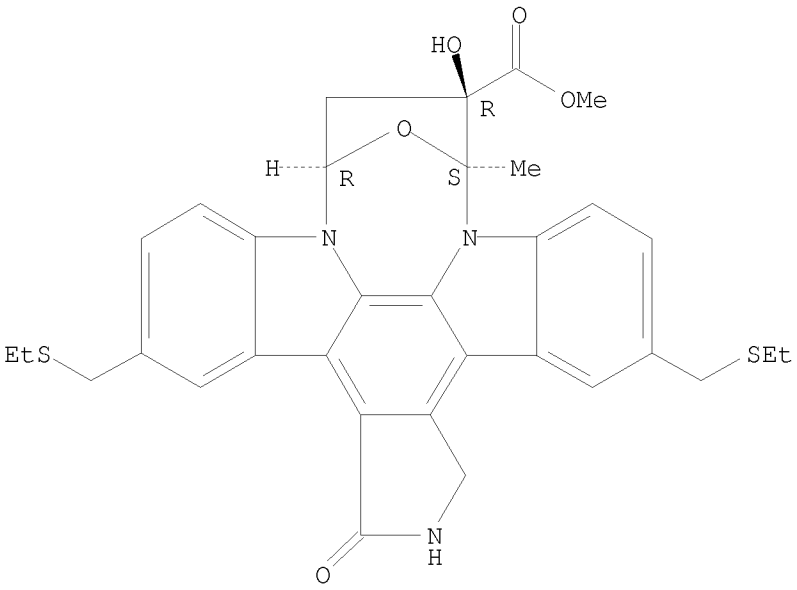
AB Staurosporine dimers RNMeCXNHX1NHCXNMeR [R = staurosporine; X = O, S; X1 = alkylene] and K-252a derivs. were prepared for use as protein kinase inhibitors for treatment of neurol. disorders. Thus, K-252a analog I [R1 =CHO, R2 = Ac] was reduced to I [R = CH2OH] which was treated with EtSH and deacetylated to give I [R1 = CH2SEt, R2 = H, II]. II attenuated the decrease in cholinergic function in the frontal cortex with induced lesions. Choline acetyltransferase in undamaged frontal cortex was unaffected by II.

IT 156177-65-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of K-252a analogs as protein kinase inhibitors)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

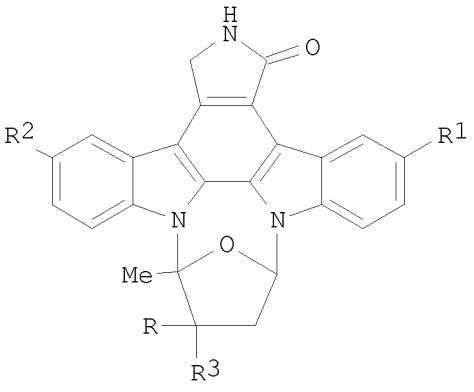
L4 ANSWER 71 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1995:958536 CAPLUS
DOCUMENT NUMBER: 124:202711
ORIGINAL REFERENCE NO.: 124:37485a,37488a
TITLE: Preparation of staurosporine derivatives as protein kinase inhibitors for the treatment of neurological disorders
INVENTOR(S): Lewis, Michael E.; Kauer, James C.; Neff, Nicola; Roberts-Lewis, Jill; Murakata, Chikara; Saito, Hiromitsu; Matsuda, Yuzuru; Glicksman, Marcie A.
PATENT ASSIGNEE(S): Cephalon, Inc., USA; Kyowa Hakko Kogyo Co., Ltd.
SOURCE: U.S., 35 pp. Cont.-in-part of U.S. Ser. No. 920,102, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5461146	A	19951024	US 1993-96561	19930722
EP 768312	A2	19970416	EP 1996-116661	19930726
EP 768312	A3	19970604		
EP 768312	B1	20000906		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AT 152111	T	19970515	AT 1993-917337	19930726
ES 2101331	T3	19970701	ES 1993-917337	19930726
EP 1002534	A1	20000524	EP 1999-120008	19930726
EP 1002534	B1	20050921		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
AT 196142	T	20000915	AT 1996-116661	19930726
ES 2151629	T3	20010101	ES 1996-116661	19930726
NZ 286198	A	20010629	NZ 1993-286198	19930726
EP 1512688	A1	20050309	EP 2004-25114	19930726
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
AT 304848	T	20051015	AT 1999-120008	19930726
ES 2248950	T3	20060316	ES 1999-120008	19930726
US 5621100	A	19970415	US 1994-329540	19941026
US 5756494	A	19980526	US 1995-456642	19950602
US 5621101	A	19970415	US 1995-486739	19950607
US 5741808	A	19980421	US 1997-800383	19970214
HK 1028206	A1	20060120	HK 2000-107421	20001121
GR 3034917	T3	20010228	GR 2000-402623	20001128
JP 2003113184	A	20030418	JP 2002-244111	20020823
JP 3723533	B2	20051207		
JP 2005170955	A	20050630	JP 2005-19891	20050127

PRIORITY APPLN. INFO.:
US 1992-920102 B2 19920724
US 1993-96561 A2 19930722
EP 1993-917337 A3 19930726
EP 1996-116661 A3 19930726
JP 1994-504731 A3 19930726
US 1994-329540 A2 19941026
US 1995-456642 A3 19950602
EP 1999-120008 A3 19991014
JP 2002-244111 A3 20020823

OTHER SOURCE(S): MARPAT 124:202711

GI



I

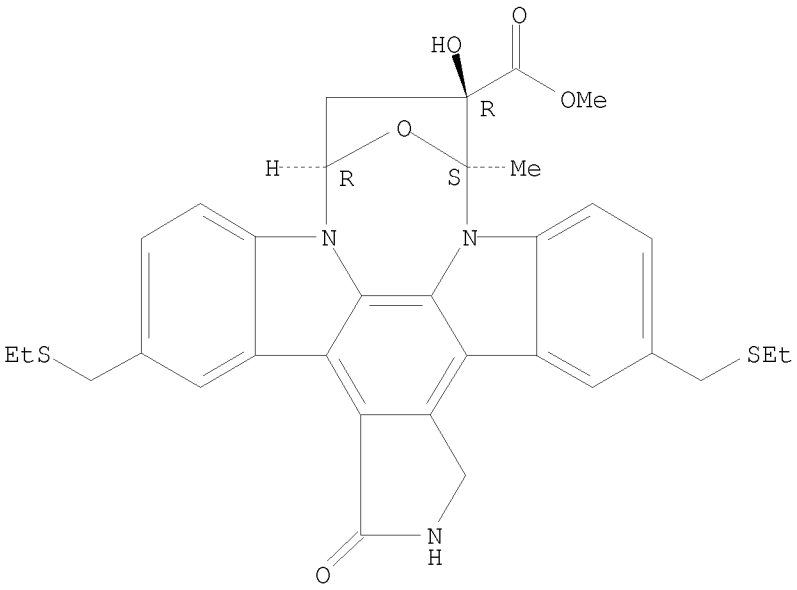
AB The K-252a, and bis-N-substituted derivs. of staurosporine I (R = HO, MeO; R1, R2 = H, Br; R3 = CH2OH, CH2NHCO2Ph, CONHPh, CH2NHCO2Me) were prepared as protein kinase inhibitors for treatment of diseased neuronal cells. Thus, N-phenylcarbamylstaurosporine was reduced with NaBH4 followed by treatment with carbobenzyloxy-L-serine and hydrogenolysis to give I (R, R1, R2 = H, R3 = CH2NH-Ser). I promoted survival of striatal neurons in the striatal cell survival assay.

IT 156177-65-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of staurosporine derivs. as protein kinase inhibitors for treatment of neurol. disorders)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



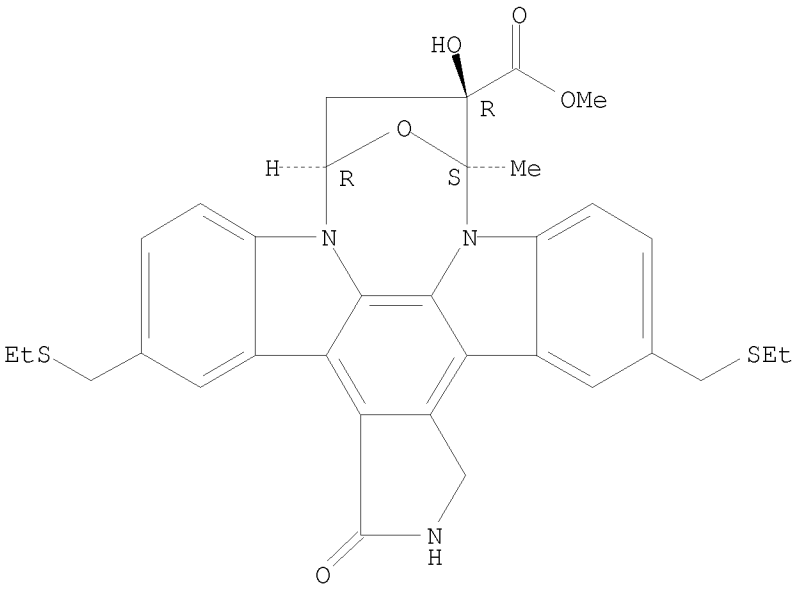
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 72 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1995:931389 CAPLUS
DOCUMENT NUMBER: 124:15478
ORIGINAL REFERENCE NO.: 124:2921a,2924a
TITLE: Aqueous indolocarbazole solutions
INVENTOR(S): Goldstein, Joel D.; Herman, Joseph L.
PATENT ASSIGNEE(S): Cephalon, Inc., USA
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9522331	A1	19950824	WO 1995-US1436	19950203
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9519110	A	19950904	AU 1995-19110	19950203

PRIORITY APPLN. INFO.: US 1994-199390 A 19940218
WO 1995-US1436 W 19950203
OTHER SOURCE(S): MARPAT 124:15478
AB Indolocarbazole solns. are disclosed. The invention features a solution comprising: (i) an indolocarbazole; (ii) a selected organic solvent being present in a concentration of between about 1% and about 99% by weight inclusive,
(iii) a dispersant being present in a concentration of between about 0.25% and about 10% by weight inclusive; (i.v.) water being present in a concentration of between 0% and about 99% by weight inclusive, and (v) a polyethylene glycol being present in a concentration of between 0% and about 60% by weight inclusive.
IT 156177-65-0P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(aqueous indolocarbazole pharmaceutical solns.)
RN 156177-65-0 CAPLUS
CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 73 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1995:777654 CAPLUS
DOCUMENT NUMBER: 123:198839
ORIGINAL REFERENCE NO.: 123:35505a,35508a
TITLE: Preparation of indolocarbazole derivatives to treat prostatic cancer and hypertrophy
INVENTOR(S): Dionne, Craig A.; Contreras, Patricia C.; Murakata, Chikara
PATENT ASSIGNEE(S): Cephalon, Inc., USA; Kyowa Hakko Kogyo Co., Ltd.
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9427982	A1	19941208	WO 1994-US6082	19940527
W: AU, CA, FI, HU, JP, KR, LK, NO, NZ, PL, RO, RU, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2163904	A1	19941208	CA 1994-2163904	19940527
CA 2163904	C	20000125		
AU 9469607	A	19941220	AU 1994-69607	19940527
AU 679752	B2	19970710		
EP 699204	A1	19960306	EP 1994-918168	19940527
EP 699204	B1	19980415		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
EP 839814	A2	19980506	EP 1998-200023	19940527
EP 839814	A3	19980916		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
AT 165097	T	19980515	AT 1994-918168	19940527
ES 2118414	T3	19980916	ES 1994-918168	19940527
JP 2002504064	T	20020205	JP 1995-501026	19940527
JP 3344586	B2	20021111		
NZ 267337	A	20050128	NZ 1994-267337	19940527
FI 9505709	A	19960103	FI 1995-5709	19951127
FI 113537	B1	20040514		
NO 9504816	A	19960126	NO 1995-4816	19951127
NO 306902	B1	20000110		
JP 2002356487	A	20021213	JP 2002-153049	20020527
JP 3727613	B2	20051214		
FI 2003001516	A	20031016	FI 2003-1516	20031016
FI 114864	B1	20050114		

PRIORITY APPLN. INFO.:	US 1993-69178	A	19930528
	US 1993-96622	A	19930722
	EP 1994-918168	A3	19940527
	JP 1995-501026	A3	19940527
	WO 1994-US6082	W	19940527

OTHER SOURCE(S): MARPAT 123:198839
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

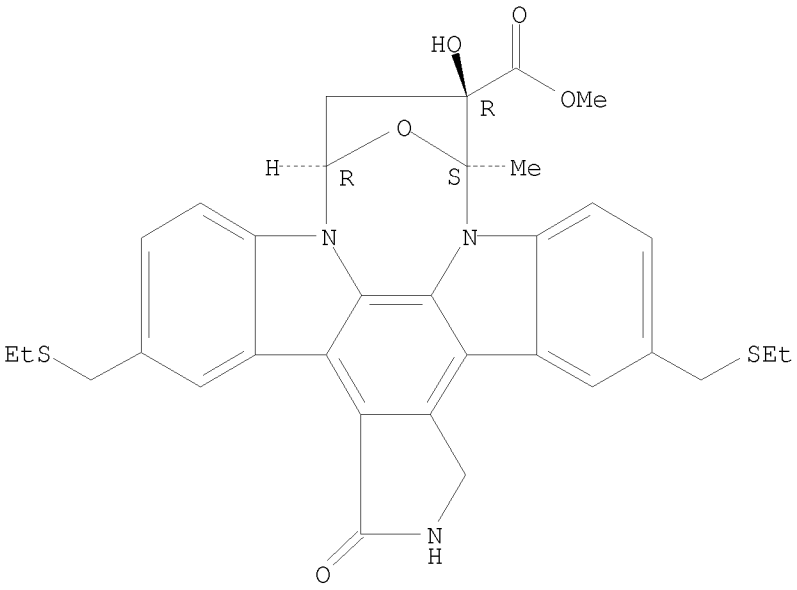
AB The title compds. [I; R = OH, alkoxy, acyloxy; R1, R2, R5, R6 = H, Cl, F, Br, I, NO2, CN, substituted ureido, etc.; X = H, CONHPh, etc.; Z1, Z2 = H, O (when combined)] [II; R1, R2, R5, R6 = H, halogen, NO2, CN, OH, substituted ureido; R3, R4 = H. alkyl, hydroxyalkyl, alkenyl; Z1, Z2 = H, O (when combined)], useful as inhibitors of tyrosine kinase activity associated with neurotrophin receptors for treating benign prostatic hypertrophy or prostate cancer, are prepared Thus, oxadiazepine I (R = OH, R1 = R2 = R5 = R6 = Z1 = Z2 = H, X = CONHCH2CH2OH) was prepared and demonstrated a IC50 of 0.038 μM against the Tsu-Pr1 human prostate cancer cell line.

IT 156177-65-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of indolocarbazole derivs. to treat prostatic cancer and benign prostatic hypertrophy from)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 74 OF 74 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1994:680945 CAPLUS
DOCUMENT NUMBER: 121:280945
ORIGINAL REFERENCE NO.: 121:51303a,51306a
TITLE: Preparation of bis-staurosporine and K-252a derivatives for enhancing neuron function
INVENTOR(S): Lewis, Michael E.; Neff, Nicola; Roberts-Lewis, Jill; Murakata, Chikara; Saito, Hiromitsu; Matsuda, Yuzuru; Kauer, James C.
PATENT ASSIGNEE(S): Cephalon, Inc., USA; Kyowa Hakko Kogyo Co., Ltd.
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

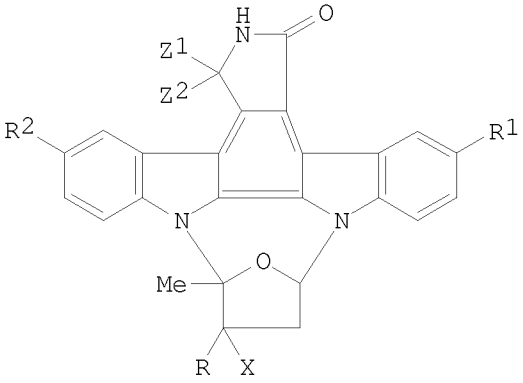
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9402488	A1	19940203	WO 1993-US6974	19930726
W: AU, BR, CA, FI, HU, JP, KR, NO, NZ, PT, RU, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9346881	A	19940214	AU 1993-46881	19930726
AU 675236	B2	19970130		
EP 651754	A1	19950510	EP 1993-917337	19930726
EP 651754	B1	19970423		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
HU 71239	A2	19951128	HU 1995-192	19930726
HU 225297	B1	20060928		
JP 08501080	T	19960206	JP 1994-504731	19930726
JP 3762427	B2	20060405		
EP 768312	A2	19970416	EP 1996-116661	19930726
EP 768312	A3	19970604		
EP 768312	B1	20000906		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AT 152111	T	19970515	AT 1993-917337	19930726
ES 2101331	T3	19970701	ES 1993-917337	19930726
BR 9306789	A	19981208	BR 1993-6789	19930726
EP 1002534	A1	20000524	EP 1999-120008	19930726
EP 1002534	B1	20050921		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
AT 196142	T	20000915	AT 1996-116661	19930726
ES 2151629	T3	20010101	ES 1996-116661	19930726
NZ 286198	A	20010629	NZ 1993-286198	19930726
EP 1512688	A1	20050309	EP 2004-25114	19930726
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
AT 304848	T	20051015	AT 1999-120008	19930726
ES 2248950	T3	20060316	ES 1999-120008	19930726
HU 225342	B1	20061028	HU 2003-1425	19930726
HU 225341	B1	20061028	HU 2003-1601	19930726
NO 9500242	A	19950307	NO 1995-242	19950123
NO 9900542	A	19990205	NO 1999-542	19950307
HK 1028206	A1	20060120	HK 2000-107421	20001121
GR 3034917	T3	20010228	GR 2000-402623	20001128
JP 2003113184	A	20030418	JP 2002-244111	20020823
JP 3723533	B2	20051207		
JP 2005170955	A	20050630	JP 2005-19891	20050127

PRIORITY APPLN. INFO.:

US 1992-920102	A	19920724
EP 1993-917337	A3	19930726
EP 1996-116661	A3	19930726
JP 1994-504731	A3	19930726
WO 1993-US6974	W	19930726
EP 1999-120008	A3	19991014
JP 2002-244111	A3	20020823

OTHER SOURCE(S): MARPAT 121:280945

GI



I

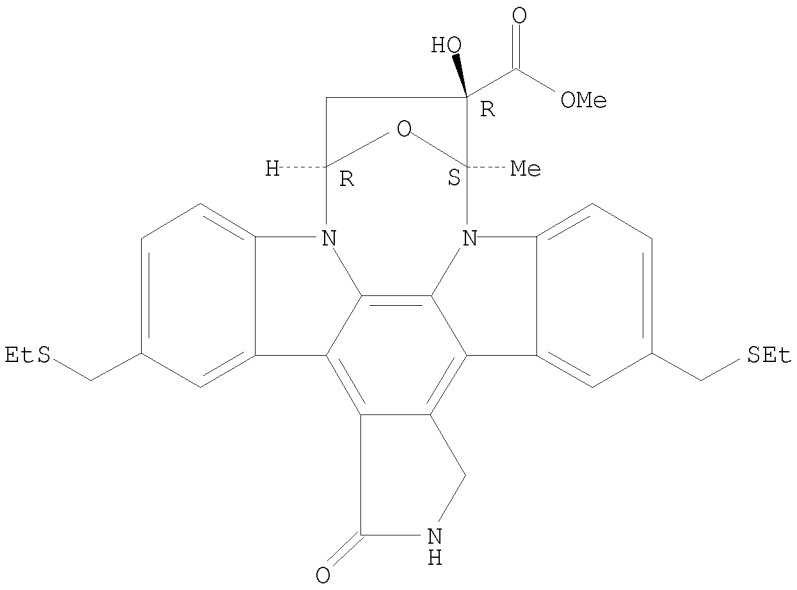
AB QNMeWNMeQ [Q = staurosporine residue; W = C(:Y)NHW'NHC(:Y); W' = C2-20 hydrocarbylene; Y = O, S], K-252a derivs. (I; e.g., R1, R2, Z1, Z2 = H; X = CH2OH; R = OMe), etc., were prepared Thus, staurosporine was treated with 1,6-hexamethylenebisisocyanate in EtOAc to give 1,6-hexamethylenebis(carbamoylstaurosporine). The latter potentiated the effect of nerve growth factor on stimulation of ornithine decarboxylase activity in PC-12 cells at all concns. tested. K-252a and numerous analogs increased choline acetyltransferase activity in fetal rat spinal cord cultures, promoted dorsal root ganglion neuron survival, etc.

IT 156177-65-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, for enhancing neuron function)

RN 156177-65-0 CAPLUS

CN 9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis[(ethylthio)methyl]-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT